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FURTHER OBSERVATIONS ON DIETARY MODIFICATION OF SERUM CHOLESTEROL LEVELS

LOUIS HORLICK, M.D., F.R.C.P.[C],*
Saskatoon, Sask.

IN A recent article in this Journal,[1] we reported that a very low fat diet (4% of calories from fat) resulted in a 20% fall in serum cholesterol levels, but was associated with a disturbance in serum lipid patterns, i.e. a rise in triglycerides and beta lipoprotein cholesterol. The addition of unmodified corn oil resulted in a return of triglycerides and beta lipoprotein cholesterol to normal levels, but serum total cholesterol was held at low levels. The low-fat period was of short duration (one week), and on this basis it was impossible to say whether the lipid transport disturbances would persist or regress spontaneously if the low-fat diet were continued. It also seemed to us important to know how much corn oil was required to prevent the lipid disturbances from occurring. This information would have considerable value in designing low-fat corn-oil diets.

Another problem in diet design was whether the corn oil added to the basal low-fat diet could be used in baking, cooking and frying without destroying its cholesterol-depressant properties. This report presents some further observations on these problems, together with our clinical experience using a low-fat corn-oil diet of our own design based on experimental studies.

MATERIALS AND METHODS

The subjects were student volunteers in good health who carried on with their regular duties during the experiments. A basal low-fat diet containing 4% of calories from fat, 16% of calories from protein and 80% of calories from carbohydrate was used throughout; varying amounts of test fats were added in exchange for carbohydrate. Caloric intake was adjusted to maintain constant body weight. Serum cholesterol, triglycerides and beta lipoprotein cholesterol were determined by methods previously described.[1]

*From the Department of Medicine, University of Saskatchewan, and the University Hospital, Saskatoon.
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RESULTS

A. *The effects of rigid fat restriction for a three-week period on the serum lipids and lipoproteins.*

Fig. 1 summarizes the results noted in three male subjects. There was a sustained decline in serum cholesterol which stabilized after 10 days on the low-fat diet (200 mg. % to 150 mg. %). Beta lipoprotein cholesterol fell more slowly at first, so

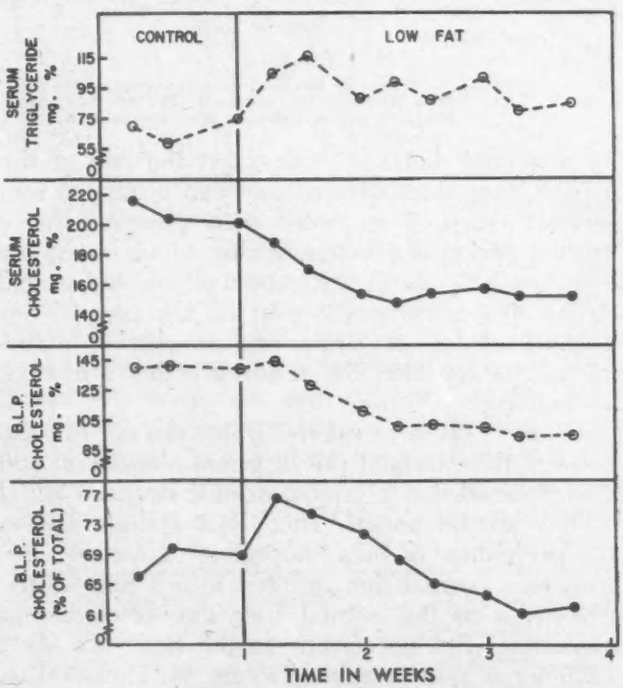

Fig. 1.—Effect of a very low fat diet (4% of calories from fat) on the serum lipids over a three-week period. Data represent the average values for three subjects. Discussion in text.

that there was an initial rise in the percentage of beta lipoprotein cholesterol. However, after the first few days, the beta lipoprotein cholesterol fell *pari passu* with the total cholesterol and the percentage of beta lipoprotein cholesterol fell below baseline levels. Serum triglycerides fluctuated, but remained above the initial values throughout the study.

B. *The effect of adding varying amounts of corn oil to a very low fat basal diet.*

Eight male subjects received the basal low-fat diet for a 10-day period. They were then returned

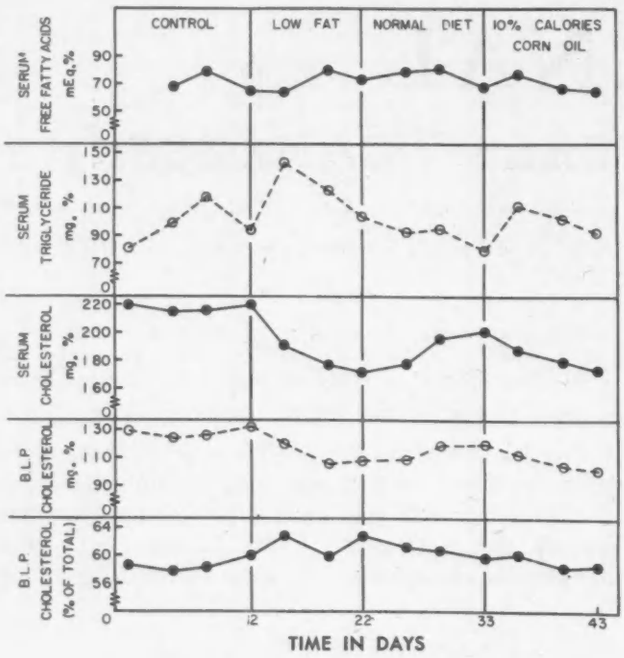

Fig. 2a

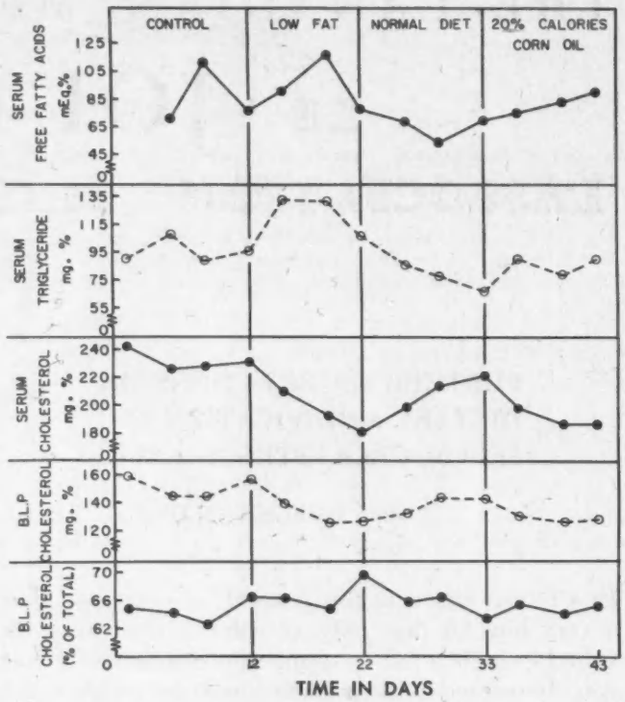

Fig. 2b

Figs. 2a and 2b.—Comparison of the effects of a low-fat diet and a diet containing 10% corn oil (2a) and 20% corn oil (2b) on the serum lipids. Data represent the average values for four subjects in each group. Discussion in text.

to a normal diet for 11 days. At the end of this period, they were divided into two groups of four subjects each. They were then observed for a further period of 10 days, during which one group received 10% of calories as corn oil and the second group 20% of calories as corn oil. The corn oil was substituted for an equicaloric amount of carbohydrate in the diet. The results are shown in Figs. 2a and b.

Group A (10% of calories from corn oil, Fig. 2a) showed the expected fall in serum cholesterol and the expected rise in triglycerides during the initial 10-day low-fat period. There was a slight rise in the percentage of beta lipoprotein cholesterol. Return to a normal diet resulted in a return of triglycerides to the normal base line level. Serum cholesterol did not return to the base line level (220 mg. %), but reached 195 mg. %. The addition of corn oil (10% of calories) was followed by a slight rise in triglycerides, but the serum cholesterol fell rapidly to the low point previously reached on the low-fat diet (172 mg. %). The percentage of beta lipoprotein cholesterol showed no rise.

Group B (20% of calories from corn oil, Fig. 2b). Initial response to the low-fat diet was very similar to that of Group A. During the control phase, the triglyceride levels returned to base line and, in fact, fell somewhat below base line. The cholesterol did not quite return to original base line levels. Resumption of the basal low-fat diet plus 20% corn oil resulted in a sharp decline of serum cholesterol levels, but in no significant rise in triglycerides or the percentage of beta lipoprotein cholesterol.

In both groups, the rise in triglyceride and the percentage of beta lipoprotein cholesterol usually seen as a reponse to low-fat diets was diminished. The result was more marked in the group receiving 20% of calories from corn oil.

C. *The effect of heating on the hypocholesterolemic properties of corn oil.*

Six subjects (five male, one female) were studied. All received the basal low-fat diet for a one-week period. For the next two weeks 40% of the calories were added as corn oil. Two subjects received the corn oil in deep-fried products (fish), two in baked form (casseroles), one as pre-heated corn oil, and one as unheated (unprocessed) corn oil. After three days on the diet, the individual Dj, who received the pre-heated corn oil, could not tolerate his diet and he was added to the group on the deep-fried corn oil diet. Spot checks were made on the cooking temperatures of the deep-fried and baked items; they ranged from 200 to 400° F. The analytical results for serum lipids are shown in Figs. 3a, b and c. Heating corn oil to the temperatures shown, 200-400° F. for short periods of time, did not impair the hypocholesterolemic response usually noted. In

TABLE I.—LOW-FAT CORN-OIL DIET IN CORONARY DISEASE

			Serum cholesterol mg.%		
			Initial	*3 months later*	
J.S.	Male	43	331	291	
D.N.	Male	44	346	212	
G.K.	Male	58	347	260	
J.W.	Male	47	380	342	
A.S.	Female	56	369	284	
T.Mc.	Male	54	365	238	
C.B.	Male	48	289	245	
W.P.	Male	52	325	236	
	Average		344	263	(−24%)

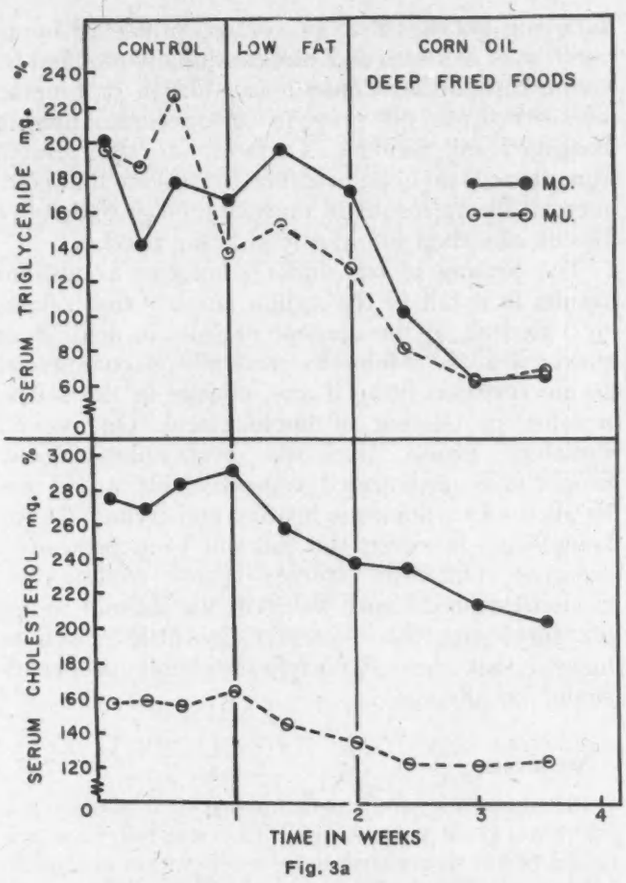

Fig. 3a

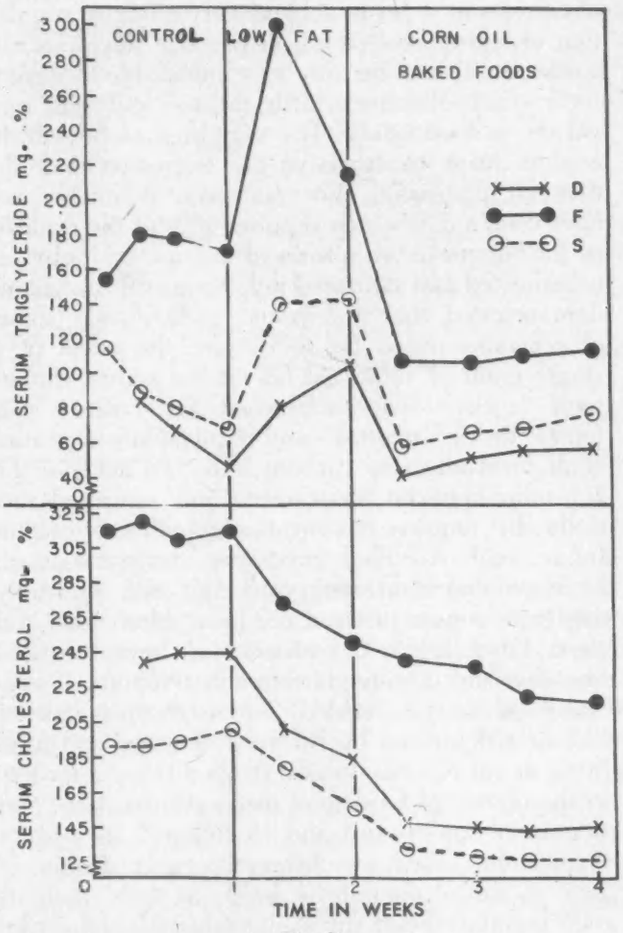

Fig. 3b

all but one instance the serum triglycerides also showed a decided decline.

D. *Clinical trial of the low-fat corn-oil diet.*

Eight patients with ischemic heart disease, all males, and with relatively high serum cholesterol levels (all but one over 300 mg. %) were followed on a low-fat corn-oil diet in which 40% of the calories were supplied as fat. Table I shows that in every instance there was a fall in serum cholesterol over a three-month period. The average decline in serum cholesterol was 24%. Because our patients are drawn from a very large area, it proved impossible to provide adequate dietary supervision for more than three months.

DISCUSSION AND CONCLUSIONS

The disturbances in the serum lipoprotein pattern previously noted after one week on a very low fat diet tended to regress when the low-fat diet was extended to three weeks. The triglyceride levels fluctuated and remained above control levels, but the per cent beta lipoprotein cholesterol fell *pari passu* with total cholesterol after the first week. In a parallel series of experiments (B), it was noted that the lipid disturbance could be prevented when 10-20% of the calories was supplied as corn oil. Thus, at least 14% of calories must be supplied as fat in order to prevent the increase of serum triglycerides and disturbances in lipoproteins which are presumably due to the great preponderance of carbohydrate in the diet. We had previously demonstrated that the increase in triglycerides could be suppressed by a variety of fats, including butter fat, margarine and corn oil, but that only corn oil kept the serum cholesterol levels down at the low values achieved on the low-fat regimen.[1]

Thus, while under ideal conditions the total amount of fat in the diet need not exceed 20%

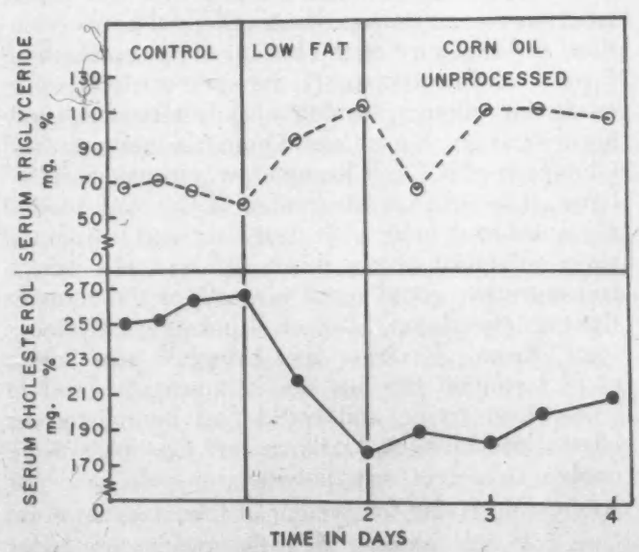

Fig. 3c

Figs. 3a, 3b and 3c.—Effect of domestic frying and baking on the hypocholesterolemic properties of corn oil. (3a) 40% of calories supplied as corn oil and utilized in deep frying. (3b) 40% of calories supplied as corn oil and utilized in baked dishes (casseroles). (3c) 40% of calories supplied as corn oil, unheated.

of calories in order to achieve very effective regulation of serum cholesterol, in practice this does not work out. This is because it is impossible to design diets which contain so little fat and still offer any variety in food intake. The very high carbohydrate content leads to excessive gas formation and abdominal distension. For our clinical studies we have used a diet which supplies 40% of the calories as fat but preserves a ratio of at least 2:1 between unsaturated and saturated fats. Keys and Anderson[2] demonstrated that it required at least two grams of polyunsaturated fat to balance the effect of a single gram of saturated fat on the serum cholesterol levels. Mono-unsaturated fat (oleic) was found to be "neutral" and equivalent in serum cholesterol effect to carbohydrate. To achieve the 2:1 ratio between unsaturated and saturated fats in the diet requires the virtual elimination of certain foods, such as dairy products, margarine, lard, hydrogenated shortenings and egg yolks, and only moderate consumption of red meat, lamb, veal and pork. Fowl, fish and seafood may be substituted liberally, and usually considerable amounts of vegetable oil must be added. This is the principle of the diets described by Brown and Page[3] and used by us in our clinical studies. It permits great variety in the choice of foods and menu construction, and is easy to understand and to follow.* In a short three-month study we observed a mean decline of 24% in serum cholesterol levels in eight patients with coronary heart disease and high initial serum cholesterol levels. Similar results have been reported by several investigators.[3-5] Choquette, Drouin-Naud and David[5] observed similar results for periods of 3-16 months with an average decline in cholesterol levels of 20.3%.

Information concerning the effect of heating during baking and frying on the nutritive properties of fats and oils is confusing and contradictory. Prolonged heat treatment of fats and oils under laboratory conditions promotes thermal polymerization, and exposure of the hot oil to the atmosphere favours auto-oxidation. If the auto-oxidation proceeds far enough, oxidative polymerization may occur. Lassen, Bacon and Dunn,[6] Kaunitz *et al.*,[7] Crampton *et al.*[8] and Kummerow and associates[9-11] have all found that oils treated in this way tended to retard the growth of test rats and contained toxic polymers which, when fed in high enough concentration, could result in death of the animals. On the other hand, Melnick, Luckman and Gooding,[12] Keane, Jacobson and Krieger[13] and Poling *et al.*[14] studied the fats and oils actually used in commercial frying and could find no deleterious effects, and Melnick, Luckman and Gooding[12] were unable to detect any polymers in oils used for potato-chip frying for periods of four days or more. One can only assume that the conditions under which commercial frying occurs in some way protect the oils from damage. Melnick pointed out that in frying potato chips the oil was protected by an inert layer of steam and was continually rectified by steam distillation. Continuous addition or topping up with fresh oil prevents the accumulation of damaged oil residues. Certainly at the present time there is no good evidence to indicate that commercial frying results in deterioration or toxicity of the oil absorbed into the food being fried.

The heating of oils under laboratory conditions results in a fall in the iodine number that relates to a decline in the content of linoleic acid of as much as 15%.[6] Melnick's studies[12] on commercial frying revealed little, if any, change in the iodine number or content of linoleic acid. One would therefore expect that the hypocholesterolemic property of unsaturated vegetable oils would not be affected by domestic heating and frying. To our knowledge, however, this has not been previously reported. Our own studies amply confirm the theoretical predictions. Whereas we did not re-use oils for frying, there seems to be little reason to believe that their hypocholesterolemic properties would be affected.

*A copy may be obtained by writing to the author.

SUMMARY

In a previous study we observed that a very low fat diet (4% of calories from fat) resulted in a sustained fall in serum cholesterol levels within one week, but was associated with a marked disturbance in serum lipid patterns (i.e., a rise in triglycerides and the percentage of beta lipoprotein cholesterol).

In the present study, prolongation of the low-fat feeding period to three weeks resulted in similar changes in the first week, but during the succeeding two weeks the beta lipoprotein cholesterol fell more rapidly than total cholesterol, so that the percentage of beta lipoprotein cholesterol fell somewhat below baseline levels. Serum triglycerides fluctuated but remained above initial values throughout the three-week period.

In order to determine the minimum amount of corn-oil supplement required to prevent the disorders in serum lipoproteins noted above, two groups of four subjects each received corn oil at levels of 10 and 20% of calories respectively for a 10-day period. In both groups the rise in triglycerides and the percentage of beta lipoprotein cholesterol were diminished, and this was most marked in the group receiving 20% of calories from corn oil.

Despite the fact that not more than 14% of calories need be supplied as fat in order to effect satisfactory reduction of blood cholesterol levels without lipoprotein disturbances, in practice such diets are unsatisfactory for long-term use because of their relative unpalatability. In our clinical studies we supplied 40% of the calories as corn oil and observed an average reduction of 24% in serum cholesterol levels in eight hypercholesterolemic subjects with coronary disease followed over a three-month period.

Since the use of corn oil in domestic cooking, baking and deep frying would permit a marked improvement in the palatability of the diet, and since no definitive information was available on the effect of such procedures on the hypocholesterolemic properties of corn oil, a separate study was undertaken. Three subjects received all their corn oil ration (40% of calories) in

deep-fried products, and two in baked products. One subject received the unheated oil only. All six subjects had a very satisfactory hypocholesterolemic response to their diets. Heating corn oil to temperatures of 200-400° F. for short periods of time did not impair the hypocholesterolemic response usually noted.

The principles arising from this study permit the preparation of satisfactory vegetable oil diets for long-term use in hypercholesterolemic states.

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EFFECT OF INTRAVENOUS DIGOXIN ON BLOOD PRESSURE, SERUM ELECTROLYTES, RENAL HEMODYNAMICS AND EXCRETORY FUNCTION IN NORMAL AND HYPERTENSIVE SUBJECTS, AND SUBJECTS IN CONGESTIVE HEART FAILURE*

H. GARFIELD KELLY, M.D., C.M., F.R.C.P.[C] and SHIU YUET WONG, M.D., *Kingston, Ont.*

INTRODUCTION

THE INJECTION of digoxin intravenously into patients with congestive heart failure has been found to produce a number of hemodynamic changes, the most noticeable of which are a rise in cardiac output[1-5] and a fall in pulmonary arterial, right ventricular end diastolic, right auricular and peripheral venous pressures.[2, 3, 5, 6] The diuretic action of digitalis has generally been assumed to be due to the increased renal blood flow which is a part of the hemodynamic action of the drug, but few data are available on the effect of digitalis on renal hemodynamics or tubular function. In 1951, Farber *et al.*[7] reported that digoxin, when injected intravenously into patients with congestive heart failure, caused an increased excretion of both water and sodium, with an associated fall in femoral venous pressure, but without any consistent increase in either renal plasma flow (RPF) or glomerular filtration rate (GFR). Digoxin had the same effect, although less marked, in patients with non-cardiac edema and in patients with compensated heart disease. Farber therefore postulated a primary renal tubular action of digoxin. In 1956, Hyman, Jaques and Hyman[8] reported that digoxin, when injected directly into the left renal artery of nine normal dogs and one dog in congestive heart failure, caused increased renal excretion of sodium, potassium and water by the left kidney but not by the right. Werkö is reported by Staub[9] to have shown that intravenous administration of lanatoside C (Cedilanid) to patients with rheumatic heart disease caused an increase in sodium excretion, RPF and GFR before any measurable increase in cardiac output.

This study was undertaken to yield further information about the action of digitalis on renal hemodynamics and tubular function in both normal and hypertensive patients, and in patients with congestive heart failure.

MATERIAL AND METHODS

Studies have been completed on 17 subjects, five of whom were normal, five hypertensive and seven in congestive heart failure. All subjects were inpatients in either the Kingston General or Ontario Hospitals in Kingston, Ontario. Studies were carried out in the morning in the fasting state, over a period of 3½ hours, and comprised the following procedures. Each patient was hydrated by being given 200 ml. of water by mouth every 15 minutes for the first hour and 100 ml. of water every 15 minutes thereafter, to ensure a good flow of urine. A brachial artery was cannulized with a Cournand needle for measurement of blood pressure and for periodic blood sampling. The urinary bladder was catheterized to ensure accurate collection of urine. Then a priming dose of 30 ml. (3 g.) of inulin and 3 ml. (0.6 mg.) of para-amino-hippuric acid (PAH) was injected intravenously, and this was followed by a sustaining infusion containing 50 ml. of inulin (5 g.) and 7 ml. of PAH (1.4 g.) in 500 ml. of normal saline solution delivered at a rate of about 35 to 40 drops a minute. After a 45-minute period of equilibration, two control urine samples were collected at intervals of 20 minutes and two blood samples at the mid-point of each urine collection. Then 1.5 mg. of digoxin was injected intravenously, and four more urine samples were collected at 20-minute intervals, with matching blood samples

*From the Department of Medicine, Queen's University, Kingston, Ont. Supported by a grant from the Ontario Heart Foundation. Reprints may be obtained by writing to: Dr. H. Garfield Kelly, Etherington Hall, Stuart Street, Kingston, Ont.

at the mid-point of each collection period. Blood and urine samples were measured for sodium, potassium, chloride, phosphorus, pH, CO_2, inulin and PAH. Urine samples were also measured for ammonia and total osmolality. Standard biochemical techniques were used throughout. Blood pressure was recorded through the indwelling arterial needle by means of a Sanborn electromanometer.

RESULTS

Blood Pressure (Fig. 1)

The intravenous injection of 1.5 mg. of digoxin caused a prompt rise in blood pressure in all three groups of patients, affecting the systolic more than the diastolic pressure, and producing a widening of pulse pressure. The rise in the control group was slight, averaging 7% for systolic pressure and 5.3% for diastolic pressure. In three of the five patients, the blood pressure had returned to control levels by the completion of the study. The increase in pressure was more marked in the hypertensive group, averaging 11.2% for systolic and 4.2% for diastolic pressure, and the duration of the rise was more sustained, persisting throughout the study. The rise in pressure was most marked in the group

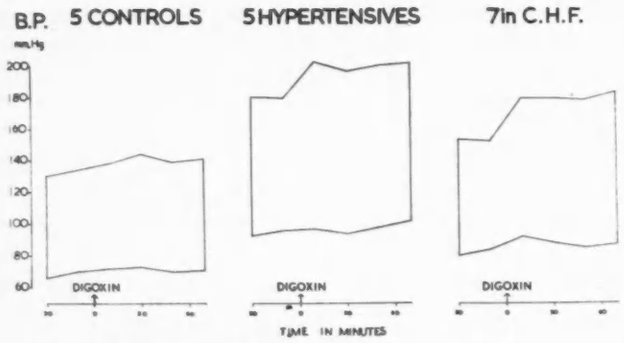

Fig. 1.—The effect of 1.5 mg. of intravenous digoxin on the blood pressure of five normal and five hypertensive subjects, and seven subjects in congestive heart failure. Digoxin caused a rise in systolic pressure and a widening of pulse pressure in all three groups, most marked in the group with congestive heart failure.

with congestive heart failure, averaging 20% systolic and 10% diastolic. Blood pressure was still rising at the completion of the study in four of the seven patients. The statistical significance of these changes is shown in Table I.

Serum Electrolytes (Table I)

Digoxin caused a prompt and consistent rise in serum potassium (Fig. 2), although the change was of statistical significance only in the group with congestive heart failure. Digoxin caused no significant change in serum sodium, chloride, pH or CO_2.

Renal Hemodynamics and Excretory Function

Digoxin caused no significant change in renal hemodynamics in the three groups of patients. Despite the rise in arterial blood pressure, RPF and GFR did not increase; rather, they declined slightly, although not significantly (Table II). The

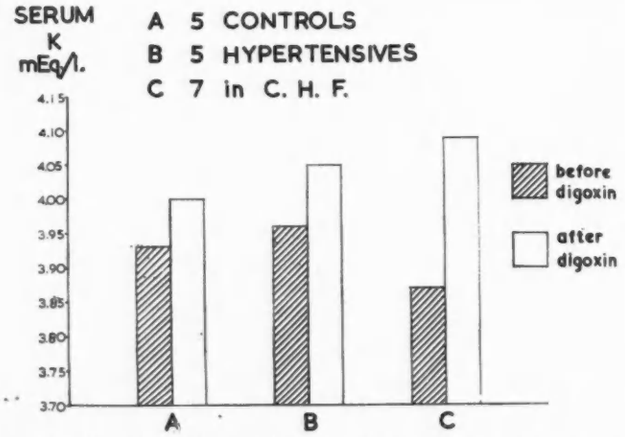

Fig. 2.—The effect of 1.5 mg. of intravenous digoxin on the serum potassium of five normal and five hypertensive subjects and seven subjects in congestive heart failure. The rise in serum potassium was most marked in the patients with heart failure.

action of digoxin on renal tubules varied slightly from one group to another, but the effects were minor and inconsistent. Excretion of sodium and chloride increased in five of the seven patients with congestive heart failure, despite the slight reduction in RPF and GFR, but the average increase was not statistically significant. There was a tendency for urinary ammonia to fall in almost all patients, but the change was statistically significant only in the normal group. Urinary CO_2 was noted to decline in the hypertensive group. A typical pattern of response to the intravenous injection of digoxin in a case of congestive heart failure is shown and contrasted with the subsequent effect of an intravenous injection of chlorothiazide in Fig. 3.

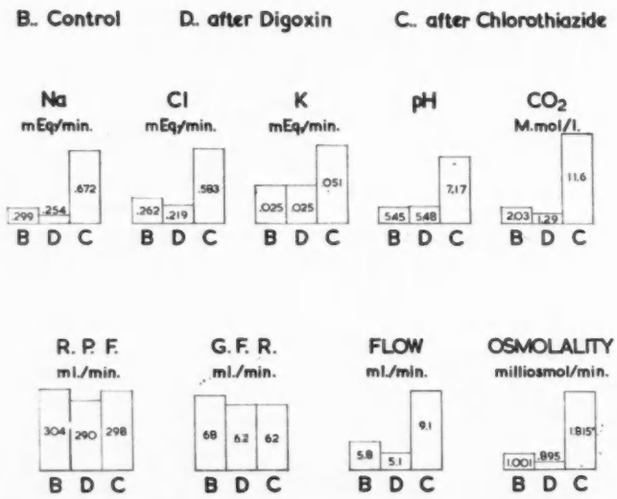

Fig. 3.—The effect of 1.5 mg. of digoxin, followed by 500 mg. of chlorothiazide (both injected intravenously), on renal hemodynamics and excretory function in a patient in congestive heart failure. Neither drug altered renal hemodynamics. Only chlorothiazide had a diuretic effect.

DISCUSSION

Blood Pressure

The evaluation of systolic blood pressure and the widening of pulse pressure noted in this study suggests that digoxin increased myocardial contractile force and improved stroke volume, not only

TABLE I.—EFFECT OF INTRAVENOUS INJECTION OF 1.5 MG. OF DIGOXIN ON BLOOD PRESSURE AND SERUM ELECTROLYTES OF FIVE NORMAL SUBJECTS

Subjects	*Age*	*pH*		*CO_2 m. mol./l.*		*Na mEq./l.*		*Cl mEq./l.*		*K mEq./l.*		*P mEq./l.*		*Blood pressure*	
		before	*after Digoxin*	*before*	*after*	*before*	*after*	*before*	*after*	*before*	*after*	*before*	*after*	*before*	*after*
W.B.	53	7.43	7.43	21.8	21.6	145.8	145.0	103.1	104.2	4.25	4.16	2.11	2.13	132/68	149/71
R.N.	48	7.41	7.41	22.6	22.4	145.0	151.7	102.4	101.9	3.75	4.03	1.95	1.99	98/48	102/49
S.M.	24	7.41	7.41	26.2	26.8	141.5	141.5	103.5	104.6	3.60	3.80	1.76	1.81	140/76	145/79
W.B.	38	7.40	7.37	27.5	27.8	142.0	141.0	98.8	100.8	4.20	4.10	1.79	2.00	136/73	142/75
K.C.	16	7.42	7.40	25.1	24.7	141.1	142.7	102.2	104.3	3.85	3.89	1.81	1.91	155/80	171/83
Average % change		−0.1		0		+0.9		+1.2		+1.9		+4.6		+7.0/+5.2	
Standard deviation		0.18		1.55		2.15		1.15		4.45		4.29		4.25/5.01	
Standard error of the mean		0.08		0.691		0.959		0.513		1.986		1.915		1.9/2.2	
P. values		0.3 - 0.20		.....		0.50 - 0.40		0.10 - 0.05		0.40 - 0.30		0.10 - 0.05		$\frac{0.05 - 0.02}{0.10 - 0.05}$	

FIVE HYPERTENSIVE SUBJECTS

		before	*after Digoxin*	*before*	*after*	*before*	*after*	*before*	*after*	*before*	*after*	*before*	*after*	*before*	*after*
H.L.	56	7.42	7.42	25.3	25.4	145.9	141.6	98.7	100.9	4.23	4.11	1.48	1.45	213/105	230/104
M.D.	50	7.37	7.38	23.6	23.7	140.0	141.0	107.5	107.9	4.04	3.99	1.57	1.63	180/93	196/95
L.L.	44	7.40	7.40	26.2	25.6	139.0	141.5	103.3	103.8	4.16	4.14	1.48	1.52	151/92	165/94
A.R.	50	7.62	7.62	24.0	24.6	147.4	145.1	103.4	105.7	3.57	3.95	1.50	1.55	176/86	200/84
D.N.	53	7.31	7.33	25.0	24.7	141.4	141.6	109.8	110.8	3.82	4.15	1.21	1.26	178/98	207/117
Average % change		+0.08		−0.04		−0.5		+1.2		+3.58		+2.3		+11.2/+4.2	
Standard deviation		0.11		1.53		1.76		0.963		6.30		2.48		3.57/8.81	
Standard error of the mean		0.05		0.68		0.79		0.43		2.817		1.11		1.59/3.93	
P. values		0.20 - 0.10		.....		0.60 - 0.50		0.05 - 0.02		0.3 - 0.2		0.20 - 0.10		$\frac{<0.01}{0.40 - 0.30}$	

SEVEN SUBJECTS IN HEART FAILURE

		before	*after Digoxin*	*before*	*after*	*before*	*after*	*before*	*after*	*before*	*after*	*before*	*after*	*before*	*after*
W.W.	79	7.26	7.27	24.2	23.9	140.0	139.5	110.0	111.5	3.89	3.95	1.39	1.48	127/65	146/66
C.W.	54	7.38	7.37	23.1	21.8	134.3	134.3	110.0	101.9	4.11	4.19	1.59	1.56	134/83	165/87
S.K.	59	7.36	7.36	18.8	19.4	138.9	137.8	104.4	106.6	4.25	4.49	1.78	1.78	150/80	180/89
A.B.	79	7.36	7.39	25.2	24.4	136.8	136.4	101.9	101.0	3.49	3.81	1.57	1.56	132/66	172/80
V.V.	65	7.47	7.47	23.9	23.7	144.3	143.9	102.6	104.3	3.68	3.95	1.79	1.83	178/98	207/117
I.H.	69	7.31	7.34	23.9	24.4	140.0	140.0	105.6	107.2	4.00	4.31	2.31	2.39	139/83	160/88
C.W.	74	7.34	7.35	24.6	24.7	141.1	141.1	109.0	110.3	3.65	3.93	1.59	1.60	181/80	209/84
Average % change		+0.13		−0.74		−0.23		+1.11		+5.80		+1.59		+19.3/+9.9	
Standard deviation		0.70		3.02		0.29		1.02		2.92		2.89		5.76/7.71	
Standard error of the mean		0.27		1.14		0.11		0.39		1.10		1.09		2.176/2.913	
P. values		0.7 - 0.6		0.6 - 0.5		0.10 - 0.05		0.05 - 0.02		0.01		0.30 - 0.20		$\frac{<0.001}{0.02 - 0.01}$	

TABLE II.—EFFECT OF INTRAVENOUS INJECTION OF 1.5 MG. OF DIGOXIN ON RENAL HEMODYNAMICS AND EXCRETORY FUNCTION OF FIVE NORMAL SUBJECTS

Subjects	Age	R.P.F. ml./min.		G.F.R. ml./min.		Urine flow ml./min.		Osmolality m. osmoles/min.		Na mEq./min.		Cl mEq./min.		K mEq./min.		P mEq./min.		pH		CO_2 m. mol./l.		NH_3 mEq./min.	
		before	after Digoxin	before	after	before	after	before	after	before	after	before	after	before	after	before	after	before	after	before	after	before	after
W.B.	53	757	736	119	105	9.6	5.9	0.993	0.911	0.329	0.302	0.224	0.224	0.034	0.036	0.047	0.050	6.45	6.20	2.2	2.0	0.101	0.089
R.N.	48	487	514	100	103	13.5	3.8	1.001	0.928	0.212	0.243	0.205	0.208	0.017	0.021	0.202	0.018	5.84	5.03	1.6	1.5	0.134	0.091
S.M.	24	661	529	70	71	7.7	7.1	0.499	0.499	0.121	0.107	0.055	0.059	0.012	0.012	0.013	0.010	6.18	6.23	2.7	3.3	0.102	0.078
W.B.	38	553	455	105	94	9.7	8.9	0.846	0.792	0.094	0.098	0.069	0.068	0.074	0.029	0.016	0.031	6.68	6.32	2.7	1.4	0.219	0.188
K.C.	16	586	446	105	90	13.2	13.0	1.246	0.949	0.261	0.215	0.270	0.191	0.035	0.024	0.016	0.018	6.61	6.56	1.9	3.0	0.173	0.119
Average % change		−11.8		−6.4		−24.0		−9.2		−3.8		−4.4		−14.6		+15.9		−4.6		+3.3		−22.8	
S.D.		12.55		7.85		29.62		8.85		13.01		14.71		33.58		45.69		5.73		39.38		9.35	
S.E.M.		5.60		3.50		13.22		3.95		5.81		6.57		14.99		20.40		2.56		17.58		4.17	
P. values		0.20 - 0.10		0.20 - 0.10		0.20 - 0.10		0.10 - 0.05		0.60 - 0.50		0.60 - 0.50		0.40 - 0.30		0.50 - 0.40		0.20 - 0.10		0.9 - 0.80		<0.01	
FIVE HYPERTENSIVE SUBJECTS																							
		before	after Digoxin	before	after	before	after	before	after	before	after	before	after	before	after	before	after	before	after	before	after	before	after
H.L.	56	375	382	77	80	6.2	6.4	1.267	1.112	0.522	0.435	0.407	0.317	0.067	0.059	0.020	0.021	7.04	7.02	12.15	9.5	0.083	0.092
M.D.	50	669	533	97	95	8.3	5.4	0.663	0.549	0.150	0.211	0.105	0.117	0.026	0.025	0.012	0.020	7.03	6.93	6.0	4.6	0.135	0.115
L.L.	44	340	253	65	53	10.0	6.4	0.784	0.639	0.160	0.126	0.150	0.115	0.042	0.030	0.022	0.023	6.55	6.61	3.12	2.94	0.094	0.081
A.R.	50	369	326	70	74	12.0	7.3	0.780	0.672	0.211	0.218	0.168	0.148	0.041	0.033	0.023	0.024	7.10	6.88	7.2	5.0	0.106	0.096
D.N.	53	294	217	63	57	14.3	11.3	1.367	0.994	0.595	0.460	0.373	0.238	0.051	0.062	0.023	0.024	5.10	4.94	6.45	5.85	0.090	0.079
Average % change		−16.3		−4.1		−25.5		−17.8		−16.5		−16.4		− 8.45		+14.4		−1.4		−19.2		−7.9	
S.D.		11.69		9.94		17.56		5.87		30.51		17.96		19.06		22.03		1.75		8.92		10.62	
S.E.M.		5.22		4.44		7.84		2.62		13.62		8.02		8.51		9.83		0.78		3.98		4.74	
P. values		0.05 - 0.02		0.5 - 0.4		0.05 - 0.02		<0.01		0.4 - 0.30		0.20 - 0.10		0.40 - 0.30		0.30 - 0.20		0.20 - 0.10		<0.01		0.20 - 0.10	
SEVEN SUBJECTS IN HEART FAILURE																							
		before	after Digoxin	before	after	before	after	before	after	before	after	before	after	before	after	before	after	before	after	before	after	before	after
W.W.	79	304	290	68	62	5.8	5.1	1.001	0.895	0.299	0.254	0.262	0.219	0.025	0.025	0.022	0.026	5.45	5.48	2.03	1.29	0.91	0.083
C.W.	54	394	421	104	113	1.3	1.3	0.700	0.642	0.085	0.094	0.066	0.097	0.042	0.035	0.047	0.042	5.31	5.43	0.20	0.20	0.133	0.114
S.K.	59	561	423	98	80	12.4	8.8	1.951	1.475	0.480	0.587	0.445	0.560	0.067	0.049	0.044	0.021	5.39	6.23	0.68	0.95	0.172	0.089
A.B.	79	419	329	99	91	1.2	4.9	0.734	0.800	0.131	0.223	0.071	0.119	0.041	0.024	0.035	0.031	6.65	6.83	1.2	4.1	0.083	0.080
V.V.	65	189	173	55	59	5.5	5.4	0.670	0.890	0.181	0.275	0.088	0.195	0.018	0.022	0.024	0.029	6.49	6.46	2.6	3.2	0.067	0.065
I.H.	69	226	189	69	54	7.5	4.7	0.744	0.712	0.148	0.182	0.190	0.189	0.038	0.042	0.016	0.016	6.33	6.04	1.6	1.1	0.093	0.067
C.W.	74	344	345	62	61	12.8	12.3	1.864	1.966	0.811	0.825	0.625	0.712	0.052	0.063	0.030	0.030	7.13	7.22	6.9	6.7	0.070	0.071
Average % change		−9.5		−6.1		+32.0		−0.06		+23.5		+37.0		−4.46		−5.0		+2.4		+47.65		−14.91	
S.D.		11.7		11.65		38.76		18.32		29.22		46.73		24.57		24.37		6.23		96.84		17.61	
S.E.M.		4.22		4.40		14.65		6.92		11.04		17.66		9.28		9.21		2.35		36.60		6.66	
P. values		0.10 - 0.05		0.30 - 0.20		0.10 - 0.05		....		0.10		0.10 - 0.05		0.70 - 0.60		0.70 - 0.60		0.40 - 0.30		0.30 - 0.20		0.10 - 0.05	

in the group with congestive heart failure where the rise in pressure was most noticeable, but in the hypertensive and control groups as well. Such an effect is in accord with recent observations. Braunwald *et al.*[10] studied the direct effects of acetylstrophanthidin and lanatoside C on the contractile force of the heart using the Walton-Brodie strain gauge arch in 21 patients with compensated heart disease, at the time of open heart surgery during cardiac bypass. Both drugs caused an increased contractile force. In our study, the rise in diastolic pressure was slight, and was statistically significant only in the group with congestive heart failure. It was probably secondary to the increased cardiac output, although output was not measured and peripheral resistance therefore cannot be calculated. One cannot entirely exclude the possibility that an arterial vasoconstrictor action of the drug might have contributed to the rise in diastolic pressure. Previous workers studying cardiovascular hemodynamics by means of cardiac catheterization have reported that intravenous digoxin had variable effects on peripheral resistance, sometimes causing the latter to rise[11, 12] and sometimes to fall.[3, 13] But Braunwald's[10] group have noted an invariable but often very transient arteriolar vasoconstrictor effect

when peripheral vascular resistance has been studied at the time of open heart surgery where it has been possible to separate the heart from the peripheral vascular bed.

Serum Electrolytes

The only change in serum electrolytes noted after the intravenous administration of digoxin was a rise in serum potassium, slight in the normal and hypertensive groups, and moderate in the group with congestive heart failure. A demonstrable rise in serum potassium in patients treated with digitalis has not been reported, but might be anticipated from the work of Lown and his colleagues[14] on dogs. They found that the injection of large amounts of acetylstrophanthidin (to the point of producing ventricular tachycardia) produced an almost invariable rise in serum potassium, averaging 0.64 mEq./l., and in addition, an almost invariable fall in serum sodium, averaging 3.1 mEq./l. In our study, the rise in serum potassium was not accompanied by an increased excretion of potassium in the urine. Previous studies on animals would indicate that the rise in serum potassium is the result of a shift of potassium from tissue cells involving particularly the liver, heart and skeletal muscle,[15-18] and in addition, a reduced uptake of potassium by skeletal muscle.[19] The much greater rise in serum potassium in the group of patients with congestive heart failure may be related to tissue anoxia; in animals[20] this has been shown to cause a shift of potassium from cells, thereby enhancing the action of digitalis.

Renal Hemodynamics and Excretory Function

It was not possible to demonstrate in this study an increase in RPF and GFR within a 90-minute period following the intravenous injection of digoxin, even in the group of patients with congestive heart failure where digitalis might have been expected to increase substantially cardiac output and thus improve renal blood flow. Nor was it possible to demonstrate a definite direct action of digoxin on the renal tubules. It is true that urinary excretion of sodium and chloride increased in five of the seven patients with congestive heart failure, despite a slight reduction in RPF and GFR, and excretion of water. These changes might indicate a renal tubular action of the drug, but they were not large enough to be statistically significant in this small group of patients. Certainly, digoxin has no effect on renal tubules comparable to that of chlorothiazide (Fig. 3). These data are in contrast to those of Farber *et al.*,[7] who found that digoxin usually produced a slight increase in both RPF and GFR, but who were not able to find any correlation between the increase, when it occurred, and the diuresis of salt and water which took place, not only in their patients with congestive heart failure, but also in patients with non-cardiac edema and in patients without edema. In the study of Hyman, Jaques and Hyman, when digoxin was injected directly into the left renal artery of a dog, producing a diuretic effect in the left kidney, it is significant that they were unable to demonstrate any diuretic effect on the other kidney.

SUMMARY

The effect of intravenous digoxin on blood pressure, serum electrolytes, renal hemodynamics and excretory function has been studied in a group of five normal and five hypertensive patients, and in seven patients with congestive heart failure.

Digoxin caused a rise in systolic pressure and a widening of pulse pressure in all three groups of patients. The changes were slight and transient in the normal subjects, more noticeable and sustained in the hypertensive subjects, and most marked in the subjects in congestive heart failure. A significant rise in diastolic pressure occurred only in the patients with congestive heart failure.

Digoxin caused a rise in serum potassium in all three groups of patients, slight in the control and hypertensive subjects, and moderate in the subjects in congestive heart failure. It caused no change in other serum electrolytes.

Digoxin had no effect on renal plasma flow or glomerular filtration rate, and no consistent effect on renal tubular function. There was a slight increase in urinary excretion of sodium and chloride in five of seven patients with congestive heart failure, but the increase was not statistically significant.

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CONTINUOUS LUMBAR EPIDURAL ANALGESIA FOR OBSTETRICS*

PHILIP R. BROMAGE, M.B., B.S., F.F.A.R.C.S.,†
Montreal

THE PAIN of normal childbirth is usually well controlled by judicious combinations of parenteral and inhalational analgesics, with perhaps the addition of a pudendal block at the time of delivery, if episiotomy and low forceps extraction are practised. However, in about 10% to 20% of patients, these measures are not enough to provide satisfactory and humane relief during protracted difficult labours, and more powerful methods of analgesia are required. Centrally acting analgesics and general anesthesia carry well-recognized hazards to both mother and child, and regional analgesics are to be preferred whenever possible.[1]

For many years low or "saddle-block" spinal anesthesia has been a popular method for delivery, but the wide publicity given to the hazards of spinal anesthesia and the incidence of "spinal" headache have caused this method to fall into disrepute for obstetrical use. Instead, pudendal and caudal block, and lumbar epidural techniques are becoming more widely used. A single injection by any of these routes provides sufficient duration of analgesia for delivery and repair of an episiotomy incision, but not for prolonged pain relief during a protracted first stage, and it is often this stage which proves the greatest trial to mother and attendants alike.

Continuous caudal analgesia, with an indwelling catheter in the sacral canal, was popularized by Hingson and his colleagues[2] at Cleveland, as a means of providing effective analgesia without depression throughout active labour and during delivery. However, there are technical and theoretical disadvantages to this technique which make it relatively unreliable; these will be discussed. In my opinion relief of pain in labour is produced more efficiently by continuous lumbar epidural analgesia. This report outlines a method which has been in use at the Royal Victoria Hospital, Montreal, during the past five years, and at the Chichester Hospital Group, England, before that. The technique appears to offer many theoretical and practical advantages for the prolonged relief of pain in difficult labour. Over 500 women in labour have been treated by this method of continuous epidural analgesia, the majority in the last two years. This number is due to the increasing popularity of the method with obstetricians and patients alike; during this period every member of the anesthetic staff has managed some cases from this series.

*From the Department of Anaesthesia, Royal Victoria Hospital, Montreal.
†Assistant Professor, Department of Anaesthesia, McGill University, Montreal.

THEORETICAL CONSIDERATIONS

Analgesia and the Pain Pathways

The pain occurring during labour is conducted along two distinct pathways.[3, 4] Appreciation and intelligent application of this dichotomous referral is essential for planning an efficient regimen of regional analgesia (see Fig. 1).

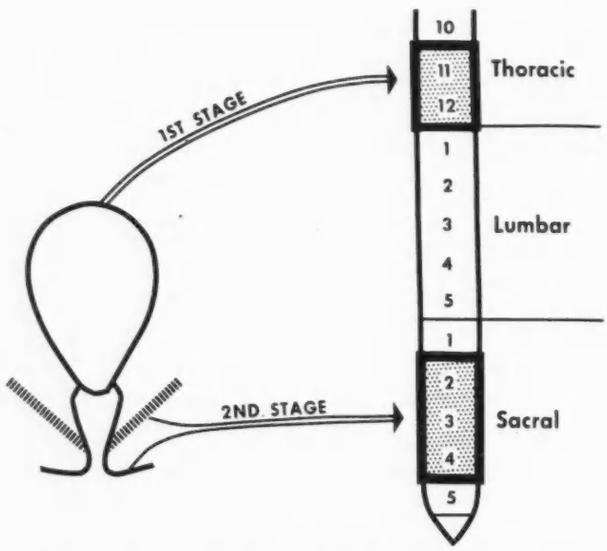

Fig. 1.—Pain pathways in labour. During the first stage of labour pain arises from the body of the uterus and is referred to the eleventh and twelfth thoracic segments. During the second stage, when the perineum is distended, pain is referred to the second, third and fourth sacral segments.

Pain from the body of the uterus during the first stage of labour is conducted to the eleventh and twelfth thoracic segments, and not to the sacral roots. In addition, some of the lumbar segments may become involved to a certain extent by direct pressure on the nerves during passage of the baby's head through the pelvic brim. At this stage not only is it unnecessary to block the sacral roots, but it is positively undesirable to do so, for their blockade will cause premature relaxation of the levator ani muscles, thus removing tone from the "pelvic gutter"; this tone is normally responsible for efficient flexion and rotation of the baby's head during descent through the pelvis. Later on, when the pelvic floor is distended by the oncoming head, perineal pain will be experienced, and the sacral segments should be anesthetized to allow painless delivery. The child can usually be delivered spontaneously by the mother's own efforts, or with the aid of forceps and episiotomy if assistance is required.

It is this order of precedence for relieving segmental pain which makes continuous caudal analgesia inferior to lumbar epidural block for obstetrics. If caudal analgesia is induced during the first stage of labour, it reverses the logical sequence of blockade, producing perineal analgesia and flaccidity too early in labour, at a time when the one is unnecessary and the other contraindicated. Besides this, if the vertebral column of the patient

has a wide lumbo-sacral angle, and if the sacral foramina are large, so much analgesic solution may leak out during caudal injection that it may never rise high enough to block the lowest two thoracic segments which are involved in the painful situation.[5] In addition, caudal analgesia carries an appreciable failure-rate even in the best hands, owing to anatomical variations of the sacrum.

Cleland[6] overcame some of these difficulties by employing both lumbar and caudal epidural catheters in combination. Two catheters were inserted early in labour, one in the upper lumbar region, and one in the caudal canal via the sacral hiatus. During the first stage of labour small doses of local anesthetic were injected through the upper catheter to anesthetize the eleventh and twelfth thoracic segments, and then, when delivery was imminent, a larger dose was injected up the caudal catheter to provide perineal anesthesia. This is a very satisfactory technique, but rather complicated, since it adds all the difficulties and uncertainties of a caudal block to the relatively easy lumbar block. Flowers, Helman and Hingson[7] adapted this technique to achieve the same result with less effort and uncertainty by using a single catheter in the lumbar region, employing posture and gravity to spread the analgesic solution to the appropriate segments in an orderly and controlled manner. We have employed this latter modification in our present series.

Analgesia and Humoral Factors

Oxytocin is the hormone from the posterior part of the pituitary gland which is responsible for uterine contractility during labour. Release of endogenous oxytocin is augmented to a certain extent by afferent stimulation from the nipples and from distension of the cervix and vagina.[8] The latter stimuli are removed by blockade of the sacral segments, and if these are blocked too early in labour endogenous secretion of oxytocin may fall off, requiring supplementation by intravenous infusion. This is likely to happen with continuous caudal analgesia, but not with properly conducted epidural analgesia.

Small increases of the circulating catecholamines, adrenaline and noradrenaline, impair the normal efficient rhythmicity of the uterus during labour. Adrenaline reduces contractile force, while noradrenaline shortens the period between contractions, thus preventing complete uterine relaxation between pains.[9] Anxiety, emotion and pain increase the output of endogenous catecholamines, and these tend to slow labour by their effects on the myometrium. On the other hand, efficient blockade of the appropriate spinal segments tends to restore normal uterine contractility under conditions of stress, by removing pain and its accompanying emotional and humoral response. This mechanism should be borne in mind when injecting analgesic solutions, and it is wise to avoid solutions containing relatively large amounts of adrenaline, in case the drug is absorbed in sufficient quantities to slow labour. For example, suppose 15 ml. of an analgesic solution containing 1:100,000 adrenaline is injected. This quantity contains 150 μg. of adrenaline and can be expected to produce absorption rates of 1 to 3 μg. per minute for a period of time. This is close to the level which will affect labour, since experimental infusions of 5 μg. per minute have been shown to produce marked depression of uterine contractility.

Analgesia and Neural Control of Parturition

In the past there has been some disagreement about the role of the nervous system in controlling normal labour. This disagreement was due in some measure to the confusion between *uterine contractility* (which is only one aspect of labour) and the whole process of expulsion, which of course involves much more than just intermittent contractions of the uterus. Skeletal muscular tone of all the abdominal compressors is deeply involved in the business of parturition, particularly the tone of the pelvic floor, and the force of contraction of the diaphragm and the abdominal muscles during the act of "bearing down". The effects of neural blockade on the extrauterine forces are likely to be very different from the effects on the smooth muscle of myometrium.

It is important for the mother to retain voluntary control of the abdominal compressors, so that she can bear down effectively during delivery. Subarachnoid blockade produces an intense degree of motor paralysis, and voluntary expulsive efforts are poor under spinal blocks which extend above the twelfth thoracic segment, owing to bulging of the flaccid abdominal wall. With epidural analgesia on the other hand, differential neural blockade is easier to achieve by using analgesic solutions which are sufficiently strong to interrupt the small pain fibres, but not strong enough to block the larger motor fibres.[10a] Under these circumstances the mother feels no pain, but is still able to contract her abdominal muscles effectively by a voluntary effort of will, even if the block extends up to or beyond the costal margin, and so she is able to retain efficient command of her extrauterine forces.

Until recently it was thought that the motor nerve supply to the uterus came from the lower seven thoracic segments, and that for this reason labour was likely to be slowed by blockade of the cord up to the fifth thoracic segment.[11] However, it should be noted that it is just these very segments and the segments below them which supply the main extrauterine forces of labour, namely the muscles of the abdominal wall and pelvic floor; besides, these segments carry afferent impulses from the sacral segments augmenting the reflex secretion of oxytocin. Recent work seems to show that the uterus is remarkably independent of direct motor innervation, uterine activity being more dependent on humoral factors. Epidural or subarachnoid blockade up to the sixth, and even the second

thoracic segment, has no direct effect on uterine tone or on the frequency and intensity of contractions, provided the blood pressure is kept within normal limits.[12, 13]

PRACTICAL APPLICATION AND TECHNIQUE

It is our practice to use the continuous epidural technique, in preference to the "single-shot" method. In this way the mother is given the benefits of restful analgesia throughout the active, and often exhausting, stages of a prolonged labour. We feel that the "single-shot" method just before delivery is not warranted, since analgesia of the perineum can be achieved quite adequately by the simpler technique of pudendal nerve block.

The lumbar epidural catheter may be inserted when labour is clearly established, and when the degree of maternal distress makes it apparent that simpler methods of analgesia will not be adequate for the safe and humane conduct of the delivery. In primiparae the cervix should be dilated 4 to 6 cm., and in multiparae 3 to 4 cm. at this time.

The patient is positioned on her side, as for a lumbar puncture, in bed or on the delivery table. A No. 17 Tuohy needle is inserted in the second or third lumbar interspace, with the orifice towards the head, and epidural puncture is performed using the loss-of-resistance technique.[10b] When the epidural space is identified 3 or 4 ml. of analgesic solution is injected. A vinyl plastic catheter is inserted up the needle, and the needle is then withdrawn over the catheter. A sterile dressing is placed over the puncture site, and the catheter is fixed to the back with adhesive tape. The patient is then quickly turned on her back and a further 3 ml. of solution is injected. The initial dose is divided in this way as a compromise between early relief of pain and the need to avoid pooling of the solution by gravity on the dependent side, for if the full dose is injected in the lateral position analgesia tends to be deficient on the uppermost side.

The pain of uterine contractions disappears in a few minutes, and a band of skin analgesia develops from about the tenth or eleventh thoracic segment to the second or third lumbar segment. Further increments of local analgesic are injected up the catheter when pain returns, the duration of analgesia depending on the drug and concentration used.

Perineal pain is felt when the fetal head distends the perineum, and this is the signal to block the sacral roots in preparation for a painless delivery. The patient is then placed in the sitting position, and 10-15 ml. of analgesic solution is injected up the catheter. The sitting position is maintained for five minutes, to allow time for the solution to percolate downwards around the sacral roots in the lower reaches of the epidural space. The patient is then allowed to lie back in a slightly head-up position on pillows, and preparations are made for delivery. Full perineal anesthesia, adequate for episiotomy and forceps extraction, takes about 15 to 20 minutes to develop from the time of injection.

The degree of segmental analgesia arising from the initial injection will have been a guide to the precise volume required at this stage.

Oxygen is always given to the mother for a few minutes prior to delivery in order to raise the pO_2 in the fetal tissues, and thereby diminish the risks of suboxygenation from any incidental obstetrical hazards, such as cord around the neck.

Analgesic Solutions

For speed of onset, intensity and all-round reliability, lidocaine hydrochloride (Xylocaine) is still the drug of choice. Mepivicaine (Carbocaine) is also very effective, and has the advantage that it lasts longer than lidocaine.

In concentrations of 1.5% to 2%, plain solutions of these drugs, without added adrenaline, do not cause a significant amount of motor blockade of the abdominal muscles. However, if adrenaline is added to prolong analgesia the degree of blockade is more intense, and a 1.0-1.5% solution should be used in order to retain effective expulsive power in the abdominal muscles.

Dosage

At term, injection of a given volume of solution into the epidural space produces a much more extensive segmental blockade than at other times. This is probably due to the space-occupying and massaging effects of distended extradural veins. With each uterine contraction blood is forced into the extradural venous plexus, as well as the caval system. The resulting rhythmic fluctuations of epidural pressure tend to spread solutions widely in the space.

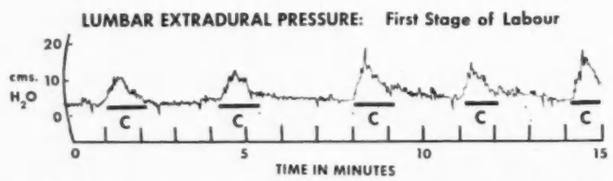

Fig. 2.—Continuous recording of pressure in the lumbar extradural space during the first stage of labour. C = periods of uterine contraction. The epidural pressure rises with each contraction owing to distension of the extradural veins by blood forced out from the uterus.

Fig. 2, taken from a continuous recording of epidural pressure during labour, demonstrates the rather high swings of epidural pressure which accompany each uterine contraction.

Care must be exercised, and dosages scaled down to allow for the extra spreading effect of this mechanism, or unnecessarily high levels of analgesia will result.

Fig. 3 shows the relationship between age and segmental spread in non-pregnant women and in women at term. From this it can be seen that dosage during labour should be about one-third less than at other times.

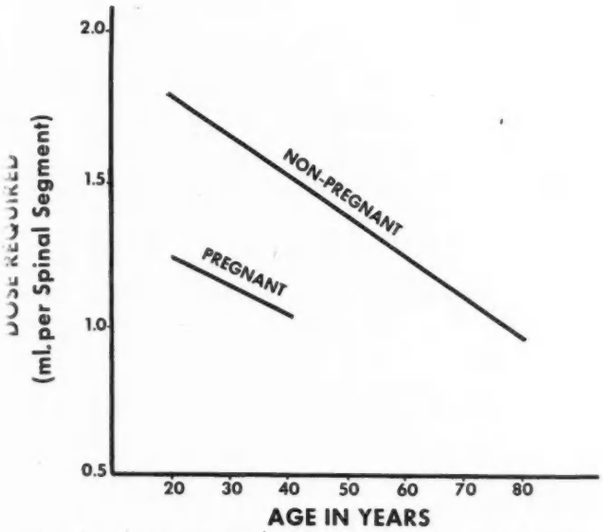

Fig. 3.—Regression lines for dose of epidural solution and age in non-pregnant subjects, and in pregnant women at term.

ADVANTAGES

1. *Comfort*

Practically the entire course of labour can be conducted painlessly, and the mother is able to enjoy the whole process in a restful and co-operative manner, without loss of efficiency to the progress of labour. When epidural block is induced in a difficult labour, after pain and anxiety have started a vicious circle of inertia and exhaustion, the change is most dramatic as tears and distress are replaced by smiling relaxation.

2. *Prolonged Effect*

Analgesia can be carried on as long as necessary once the epidural catheter is in place. In cases that require oxytocic infusions there is no contraindication to administering a continuous epidural block, when a Pitocin dip is running at the same time.

3. *Control*

Spread of analgesia is easily controlled by posture, and by using the right volumes of epidural solution at the right time. In this way analgesia is confined to the appropriate spinal segments, and labour is not slowed by premature relaxation of the pelvic floor, or by paralysis of the abdominal muscles.

4. *Lack of Depression*

The mother remains alert and co-operative during labour, and the use of centrally acting depressants, such as meperidine (Demerol), is unnecessary. At birth the child is not depressed and cries lustily, and the mother is able to enjoy full participation in the act of childbirth.

5. *Versatility in Special Circumstances*

(a) CESAREAN SECTION

The anesthetic management is simple in cases where a trial of labour proceeds to Cesarean section. It is only necessary to inject further increments of analgesic solution up the epidural catheter, until skin analgesia reaches the costal margin. The patient is then ready for operation.

(b) ECLAMPSIA

In eclampsia the risks of sudden death or permanent damage to the kidney make it essential to lower the blood pressure and improve renal blood flow as quickly as possible.[14-16] If labour is in progress, delivery should be expedited under optimal conditions. The following case illustrates how these requirements can be met by continuous epidural analgesia, after sedative treatment has failed.

A woman aged 27 years who was pregnant for the second time had a normal antenatal course until the expected date of delivery. Slight labour pains began one week after her expected date and these were quickly followed by severe frontal headache. She was admitted to St. Richard's Hospital, Chichester, on September 16, 1954, with a blood pressure of 180/100, gross edema, oliguria and albuminuria. She was given 30 mg. of morphine sulfate and 1.8 g. of potassium bromide with 1.2 g. of chloral hydrate. Three hours after admission she had a major convulsion, followed by a second 90 minutes later; twitchings persisted after the convulsions and further seizures seemed certain.

Light general anesthesia was administered in order to quiet the patient sufficiently to carry out epidural puncture. Twenty millilitres of 1.0% lidocaine was injected into the extradural space between the second and third lumbar vertebrae, and an epidural catheter was inserted. Following this the blood pressure fell precipitously to 70/40 mm. Hg, and it was necessary to give methyl amphetamine (Methedrine) intravenously to raise the blood pressure to normal levels. The patient awoke feeling refreshed, relaxed, and free from headache. No further twitchings or seizures occurred. Labour progressed, and two additional injections of 1.0% lidocaine were given up the epidural catheter. Three hours after inducing the block the cervix was fully dilated, and perineal analgesia was adequate for forceps delivery of a live child. The urine was clear of albumin 40 hours later, and the patient made an excellent recovery.

As Bryce-Smith and Williams[15] point out, when epidural blockade is prolonged for many hours or several days, successive injections tend to become progressively less effective. It is then necessary to increase the volume of epidural solution at each injection, in order to maintain the sympathetic blockade at a level high enough to reduce the blood pressure. If this fails, the technique should be abandoned in favour of other methods, such as continuous subarachnoid block, or intravenous infusions of hypotensive drugs.

DISADVANTAGES AND DANGERS

1. *Vascular Hypotension*

Too extensive a block, with resulting sympathetic paralysis, may cause undesirable drops in blood

pressure. With proper technique this happens only very rarely; nevertheless, the blood pressure should always be watched carefully, and a suitable pressor drug should always be ready at hand and drawn up in a syringe, in case it is required.

2. *Toxic Reactions to Local Anesthetic Drugs*

Injection of a local anesthetic drug anywhere in the body carries the remote risk of relative overdosage from accidental injection into a vein, or from rapid vascular absorption. Solutions without adrenaline added to them are absorbed quite readily from the extradural space, and large doses may give rise to appreciable concentrations in the blood, sometimes reaching nearly halfway to the toxic threshold, which in the case of lidocaine is about 10 μg./ml.[17] High concentrations of local analgesics in the blood stream appear to depress uterine activity, probably by direct action on the myometrium. In our department, we have analyzed the content of lidocaine in the venous blood after epidural injection of the 2% solution. We have found that with proper technique, doses up to 7 mg./kg. of body weight of the plain solution provide a wide margin of safety. If adrenaline is added in a concentration of 1:250,000, the dosage of lidocaine may be increased to 10 mg./kg. These quantities are in excess of amounts which would be required clinically.

If large doses of lidocaine are given to the mother, measurable quantities may pass across the placenta into the fetal circulation, but we have not found any evidence of fetal depression from this cause. Our largest recorded concentration of lidocaine in fresh cord blood has been 3.0 μg./ml., a level which is well below the toxic threshold.

3. *Slowing of Labour*

The nervous and humoral mechanisms of labour have been discussed. With correct management the continuous epidural technique provides better relief of pain, and is less likely to interfere with the progress of labour than any other method of analgesia. However, if excessive amounts of local analgesic solutions are injected too early in labour, blockade may spread to the sacral segments prematurely, causing a lax perineal floor, with inefficient flexion and rotation of the fetal head.

4. *Sepsis*

Imperfect aseptic precautions may introduce infection into the extradural space. Metastatic epidural abscesses occasionally appear spontaneously following infection elsewhere in the body, but I am not aware of any reported cases arising from the lumbar epidural analgesia. However, infection remains a possible hazard if careless technique is used, although it is a more remote danger than in caudal analgesia, where injection is made into a potentially contaminated area.

5. *Skill Required*

Continuous epidural analgesia is not a technique for the occasional anesthetist, and its use should be confined to institutions with proper staffing facilities. Although epidural puncture in itself is relatively easy, given care and a good pair of hands, the management of the continuous technique in labour does require a degree of skill and judgment which is unlikely to be attained without special training and experience.

SUMMARY

The theoretical background of conduction analgesia for obstetrics is discussed, and the role and management of continuous epidural analgesia are outlined on the basis of experience with its use in the management of over 500 women in labour.

The technique can provide continuous relief of pain from the time that labour becomes properly established until delivery is complete. With proper management, the forces of labour are not depressed. Once an epidural catheter is in place, analgesia can be extended at short notice in order to carry out emergency procedures such as Cesarean section, without further inconvenience to the patient. Thus it becomes the anesthetic of choice for difficult labours, and trial of labour.

Continuous epidural analgesia is not warranted for normal simple delivery in multiparous patients, where simple methods of analgesia are usually sufficient; indications for its use arise in only about 10 to 20% of all deliveries.

My thanks are due to Dr. D. E. Crowell for carrying out blood lidocaine estimations, and for his help with the recording in Fig. 2.

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THE TRABECULAR PATTERNS OF THE NECK OF THE FEMUR WITH PARTICULAR REFERENCE TO CHANGES IN OSTEOPOROSIS*

MICHAEL C. HALL, Ph.D., F.R.C.S.[C],
Toronto

THE PATTERNS of the trabeculae in the upper end of the femur have been a subject of research for many years. They were well illustrated by Wolff nearly a hundred years ago, and have remained of interest since that time owing to the frequency of fractures in this region. The appearance of the trabeculae in the coronal plane (Fig. 1) is

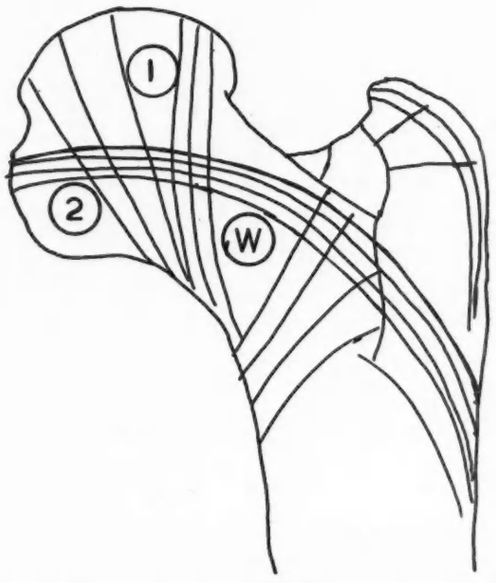

Fig. 1.—The appearance of the trabeculae in an antero-posterior roentgenogram. (1) is the primary vertical group of trabeculae, (2) the secondary transverse group, (W) is Ward's triangle.

described in most standard works on this subject. Sections made along the neck of the femur were illustrated by Dixon[3] and Carey[2] and more recently by Harty.[5] Sections through the neck in a sagittal plane do not seem to have found the same favour.

The interest of surgeons in this area lies in both the etiology and treatment of fractures through it. The former subject is reviewed by Hirsch and Frankel,[6] and the latter is covered in a recent symposium.[7] The density of the pattern of trabeculae is important in regard to the strength of bone which would resist the occurrence of a fracture, and is also important in the most advantageous placing of metallic internal fixation should such a fracture occur, although simple mechanical principles[4] and vascular supply[1] must also be considered. Not only is the normally occurring density of significance but consideration must also be given to the physiopathological changes accompanying ageing which probably constitute one of the most significant factors in the etiology of fractures at this site. Urist[9] reported that in 76% of patients with a fracture of the hip under his care there was osteoporosis of such a degree that vertebral collapse had occurred. He wrote, "The cortex is reduced to a thin shell." In any bone there are two major groups of trabeculae (as illustrated in Fig. 1). The primary trabeculae run parallel to the lines of force transmitted through the bone, and resist static distortion. The secondary trabeculae are oblique to the primary trabeculae, and resist dynamic distortion. In the presence of osteoporosis, since there is a generalized loss of volume of bone matrix, the remaining tissue becomes organized in such a way that the maximum bone tissue is concentrated in the primary trabeculae. This occurs at the expense of the secondary trabeculae which undergo atrophy to the point of disappearance. This process, commonly noticed in the spine, has been well illustrated by Schmorl and Junghanns.[8] In the upper end of the femur the degree of osteoporosis can be estimated by this change, and an antero-posterior radiograph, of reasonable quality, taken to demonstrate the fracture of the hip, will show the extent of the change in the unbroken femur. To estimate the changes in the upper end of the femur in osteoporosis, a study has been made of the patterns of trabeculae in normal and abnormal bones.

MATERIAL

Thirty femora of unknown age and history were chosen at random from the stock of the University of Toronto Department of Anatomy. They were examined radiologically while intact, and the upper ends were then sectioned in the sagittal, coronal or horizontal planes. The slices of bone, about a quarter of an inch thick, were also radiographed.

Fig. 2.—The antero-posterior appearance of Group 1 normal bone, showing equal development of primary and secondary trabeculae.

*From the Department of Anatomy, University of Toronto.

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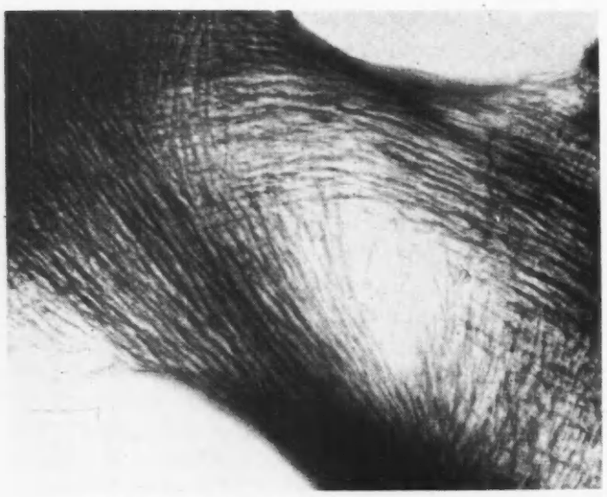

Fig. 3.—Detail of neck of femur of Group 1.

Fig. 4. — The antero-posterior appearance of Group 2, mildly osteoporotic, bone showing that secondary trabeculae are about half as distinct as the primary trabeculae.

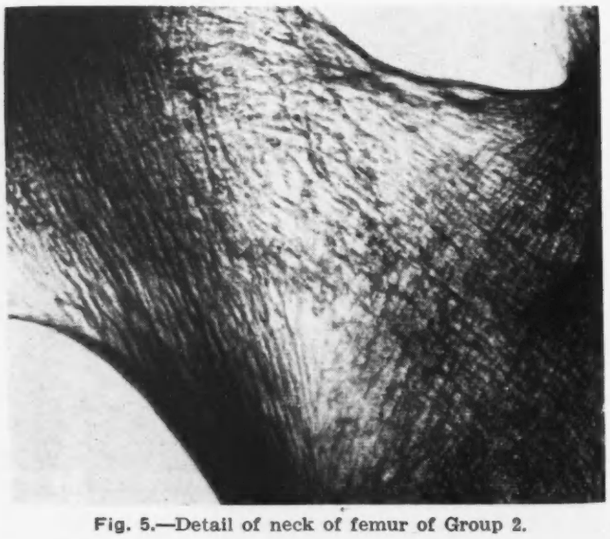

Fig. 5.—Detail of neck of femur of Group 2.

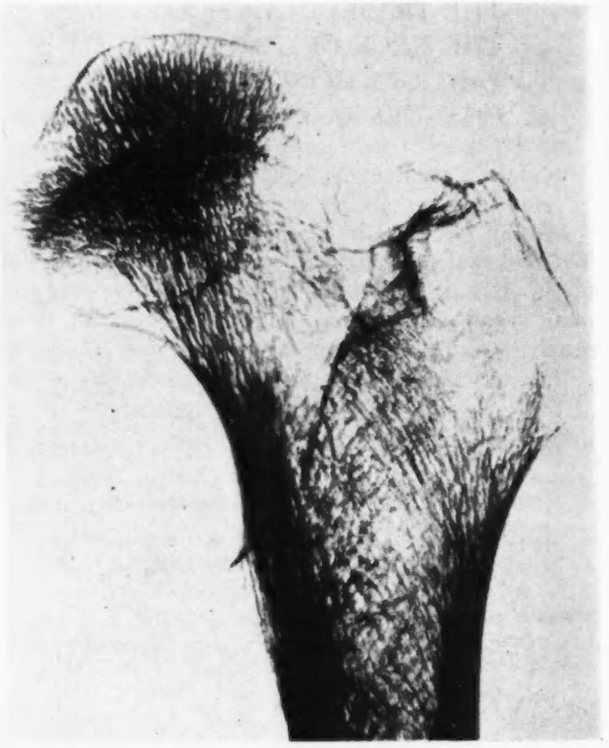

Fig. 6.—Antero-posterior appearance of markedly osteoporotic Group 3 bone; the secondary group of trabeculae are scarcely discernible.

RESULTS

A comparison of the appearance of the secondary arciform trabeculae with the primary vertical trabeculae allows an easy division of the bones

Fig. 7.—Detail of neck of femur of Group 3.

into three groups on the basis of their antero-posterior radiological appearance:

GROUP 1. — Equal development of the two rays of trabeculae, which is believed to be the "normal" state (Figs. 2 and 3).

GROUP 2. — The secondary trabeculae are about half as dense as the primary trabeculae (Figs. 4 and 5).

GROUP 3. — The secondary trabeculae are scarcely seen on the radiograph (Figs. 6 and 7).

Sections in the sagittal plane, i.e. vertical and at right angles to the axis of the neck, are shown from these same bones (Figs. 8-10). The round section is mid-cervical, and the oval one is from the base of the neck. The amount of greater trochanter seen represents only the degree of overhang of this structure, and does not indicate any difference in the point of section in the neck of the various bones.

GROUP 1. — Section through the base of the neck (Fig. 8a) shows the cortex to be thick anteriorly, posteriorly and inferiorly. Within the lumen of the section the commencement of the primary trabeculae is seen inferiorly; it is separated, by an area of bone of low density known as "Ward's triangle",[10] from the secondary trabeculae occupying the upper one-third of the lumen. The circular mid-cervical section (Fig. 8b) shows a more even thickness of well-formed cortex, and a greater area of the lumen occupied inferiorly by the primary trabeculae. The secondary trabeculae form a hood, lying anteriorly, posteriorly and superiorly in the neck. They surround Ward's triangle which lies centrally, and which, although not as dense as the bone elsewhere, is not empty.

GROUP 2. — There is a thinning of the cortex generally (Fig. 9); this is especially noticeable anteriorly. Primary and secondary trabeculae are apparent in both sections, but are more scanty than in Group 1; Ward's triangle, however, is not more obvious.

GROUP 3.—The cortex has become thinner still (Fig. 10), retaining its greatest thickness postero-

Fig. 8.—Sagittal sections through the neck of femur in Figs. 2 and 3; (a) is through the base of the neck and (b) through the mid-cervical region. The cortex is dense and thick; the trabeculae are close-knit; Ward's triangle is apparent.

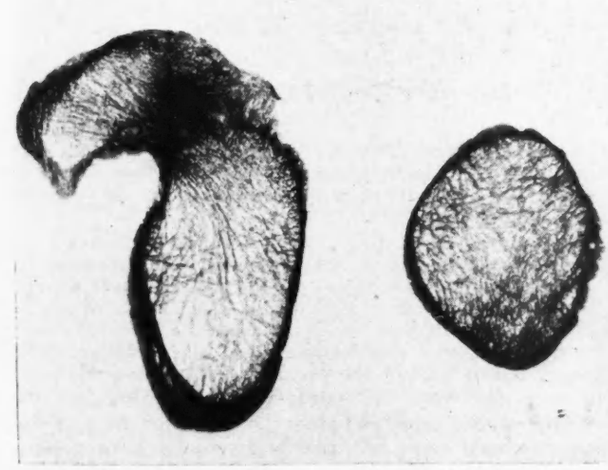

Fig. 9.—Sagittal sections through bone in Figs. 4 and 5. The cortex is thinner and the trabeculae more scant.

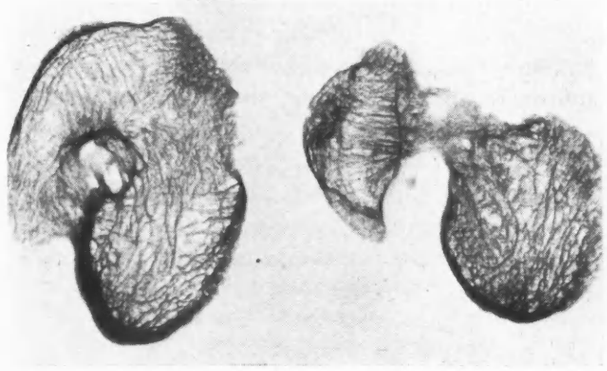

Fig. 10.—Sagittal sections through bone in Figs. 6 and 7. The trabeculae are markedly thin, the cortex is markedly reduced in width particularly anteriorly, but there is no central cavity in the neck.

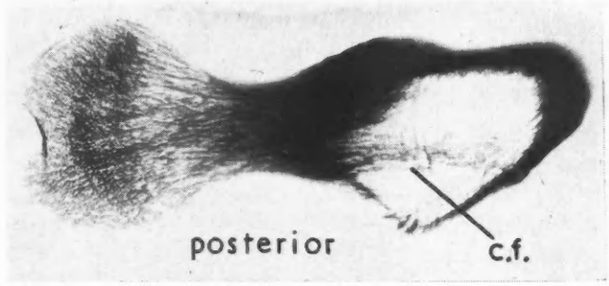

Fig. 11.—Horizontal section along axis of femoral neck, at inferior surface. Calcar femorale is seen extending from neck to shaft (c.f.).

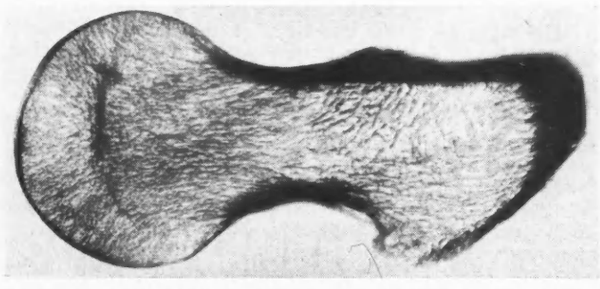

Fig. 12.—Section made at a level above that of Fig. 11. Secondary trabeculae are seen arising from shaft cortex, and primary trabeculae from neck cortex.

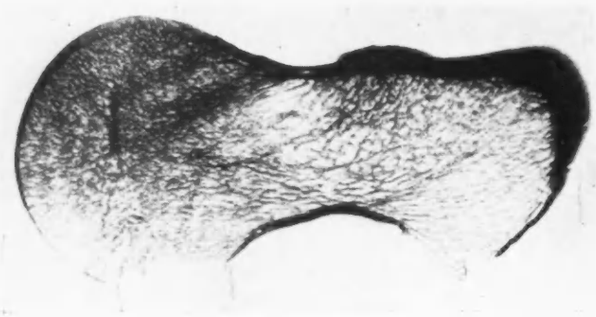

Fig. 13

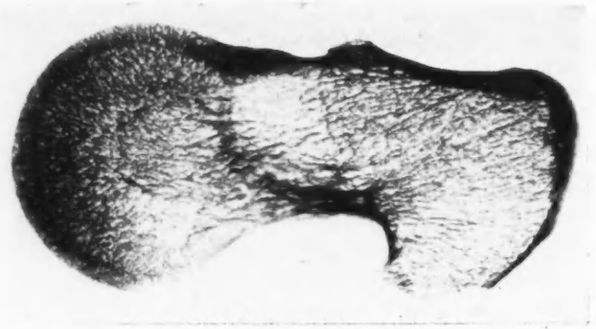

Fig. 14

Figs. 13 and 14.—Made at a level above that of Fig. 12, and showing maximum trabecular density posteriorly in the neck.

inferiorly. The trabeculae are more scanty, but again, although there is less bone centrally, the femoral neck is not hollow. The quality of bone, however, is quite inadequate to resist the movement of a nail.

A femur, believed to be normal from its trabecular appearance, was sectioned horizontally in the plane of the femoral neck (Figs. 11-14). It is seen that the area of minimum bone density is situated anteriorly in the neck, and that the posterior neck is well filled with both primary and secondary trabeculae. The upper part of the much misrepresented calcar femorale[5] is seen, in Fig. 11, as a line continuing the posterior cortex of the neck through the lesser trochanter to the posterior cortex of the shaft.

CONCLUSION

In osteoporosis of the neck of the femur, as elsewhere in the body, the bone remodels so that maximum resistance is offered to static loading. The secondary trabeculae are scant but the neck of the femur does not become hollow. The cortex undergoes marked atrophy, particularly anteriorly.

SUMMARY

The sections of 30 cadaveric femora sectioned in various planes were examined radiologically. The appearance of the standard primary and secondary trabeculae of the femoral neck is described. The atrophy that occurs with osteoporosis is seen mainly in the secondary trabeculae. However, radiographs of sagittal sections through the neck of the femur show that this atrophy does not leave a cavity in its lumen. Cortical thinning is found to the greatest extent in the anterior surface of the neck.

I wish to express my appreciation to Professor J. W. A. Duckworth in whose department this study was performed, and to the Canadian Arthritis and Rheumatism Society and the J. P. Bickell Foundation from whom grants are received.

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PAGES OUT OF THE PAST: FROM THE JOURNAL OF FIFTY YEARS AGO

RETROSPECT OF SURGERY

The statistics of the mortality of appendicitis during the past ten or fifteen years is one of the most striking things in modern surgery. Where there was, ten years ago, a mortality of 8 per cent. in operations done within the first forty-eight hours, on a comparatively small number of cases, the mortality now—in a series five times as great—has dropped to 6 per cent. and with some surgeons even to the zero mark. Taking all classes of cases operated upon, at all stages of the disease, where fifteen years ago a mortality of 22 per cent. was registered, last year, in a series ten times greater in number, the mortality was reduced to 2.2 per cent., thus making the results just one hundred times better than a few years ago. Yet, there are still some surgeons who endeavour to differentiate between a catarrhal and a gangrenous appendicitis, forgetting for the time all the possible stages between the two; forgetting also that a benign case may pass rapidly into a grave condition before such procrastinating surgeon can make up his mind as to the path of safety.

Another advance during the past year has been the almost universal use of iodine in the preparation of the field of operation. This procedure has done much towards the greater success in the treatment, particularly of severe, lacerated wounds and of compound fractures. Formerly a surgeon was not content with the dirt worked into the wound at the time of the accident, but must needs scrub in more dirt from the surrounding skin. Surgeons, too, are appreciating more and more the danger of the exploring finger in such cases, and are beginning to learn the advantage to be gained from doing as little as possible.—*Canad. M. A. J.*, 1: 1101, 1911.

SPECIAL ARTICLE

NEW DRUGS IN PSYCHIATRIC THERAPY*

H. E. LEHMANN, M.D.,† *Montreal*

INTRODUCTION

TRANQUILLIZERS and antidepressive drugs are a fairly recent addition to the therapeutic armamentarium of medicine. These agents can be conveniently discussed under the general heading of psychotropic drugs, which are defined as drugs which have a direct influence on behaviour, perception, mood or thought processes. A number of psychotropic drugs fitting this definition have been known and used by man for a considerable time. Alcohol, caffeine and certain narcotics are the oldest pharmacological agents of this type. The first discovery of their properties is lost in the dawn of recorded history. With the advent of scientific medicine, systematic research during the past 100 years has led to the development of anesthetic and analgesic drugs and later to the introduction of a variety of hypnotic and sedative agents. It was only natural that the first remedies developed were for the universal ills of mankind, that is, pain, insomnia and anxiety. Effective drugs for more specific uses in the treatment of mental and emotional disorders have been systematically developed only in the last ten years, to be exact since 1952, when Delay and Deniker in France administered chlorpromazine for the first time to agitated psychotic patients and noted its extraordinary tranquillizing effect.

The public reaction to the new drugs which followed chlorpromazine and which have been variously referred to as tranquillizers, neuroleptics, ataractics, energizers and antidepressants, can be divided into three phases:

The first phase of *impact* has been characterized by the *surprise reaction* of the medical profession to the utterly unexpected therapeutic effects of these drugs.

The second phase of *publicity* has been marked by *confusion* when the general public, the newspapers and big business were taken over by the "tranquillizer boom".

The third phase, which we seem to have entered by now, is that of *research*, which is gradually increasing the available amount of systematic and useful information.

The need for a rapid increase in research efforts in this field has led to the development of a new scientific discipline during the last decade. This new area of research, called psychopharmacology, is a complex interdisciplinary blend of pharmacology, psychology and psychiatry.

It has now become impossible to give a comprehensive survey of existing drugs in the field of psychopharmacology within the confines of a reasonably brief paper, although this was still quite feasible only three or four short years ago. Today one would only succeed in creating confusion when attempting to describe the individual properties of each psychotropic pharmaceutical on the market.

This discussion will, therefore, restrict itself to an outline of some of the fundamental principles that underlie the indications for and application of therapy with psychotropic drugs, in the hope that the reader can evaluate more critically the many claims which are being made in the pamphlets and publications which deal with these new drugs. Such material finds its way to the doctor's desk almost every day.

CLASSIFICATION OF PSYCHOTROPIC DRUGS

It is possible to divide psychotropic drugs into five principal categories according to the main psychiatric syndromes which require treatment. These five categories, in turn, refer to three basic parameters of psychological functioning. The three basic parameters are: (1) arousal, (2) mental integration and (3) mood. Oriented toward the two extremes of the arousal parameter, there are two psychotropic drug categories: *stimulants* and *sedatives*. The stimulants aim at increasing and the sedatives at reducing psychic arousal. Figs. 1 and 2 indicate the effects of these drugs. Fig. 1 is the drawing of a house made by a woman, before and two hours after receiving 7.5 mg. of Dexedrine. Note the considerable increase in detail, pressure and general energy output expressed in the second drawing, which was done after she received the stimulant. Fig. 2 shows the effects of three grains of sodium amytal on another woman. She was also asked to draw a house before, and again two hours after receiving the drug. Here we see the reverse of the first illustration. A definite decrease of energy output has taken place as the sedative effect of the barbiturate produced a lessening of pressure, a reduction of detail and size of the drawing. In general the drawing is a more inhibited and less elaborate graphic expression.

Turning now to the parameter of mental integration, certain psychotropic drugs can be considered under the categories of *antipsychotic* and *psychotogenic* effects. Antipsychotic drugs are defined as pharmacological agents which have a therapeutic effect on symptoms of a specifically psychotic nature, such symptoms as hallucinations, paranoid delusions or the autistic thought disorder which is present in many patients with schizophrenia. Until 1952 no drug was available which could be relied

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*From the Verdun Protestant Hospital, Verdun, Que., and McGill University, Montreal.
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†Clinical Director, Verdun Protestant Hospital; Associate Professor of Psychiatry, McGill University.

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Fig. 1.—The effects of a stimulant, illustrated in two drawings made by a subject immediately before (A) and two hours after (B) the administration of 7.5 mg. of dextro-amphetamine sulfate (Dexedrine).

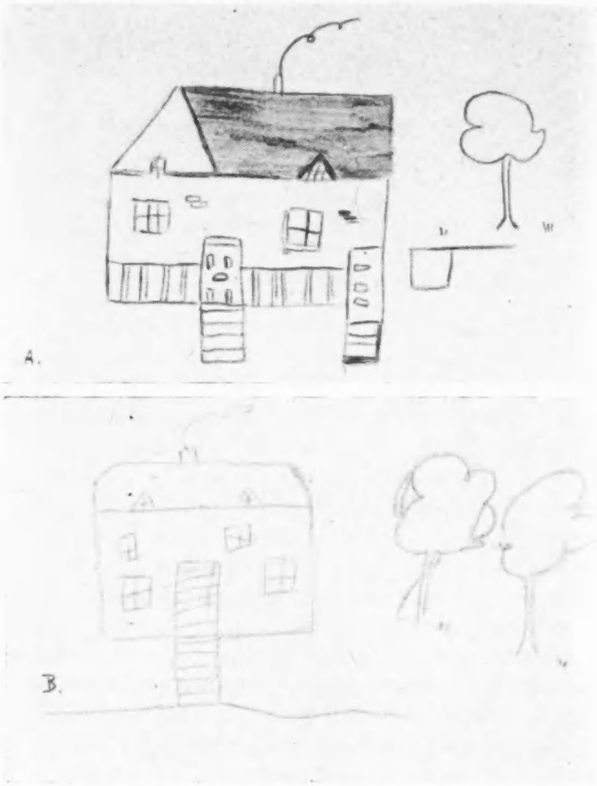

Fig. 2.—The effects of a sedative as illustrated in two drawings made by a subject immediately before (A) and two hours after (B) the administration of 3 grains of sodium amytal.

upon to exert specific therapeutic effects on such psychotic symptoms, which are manifestations of a severe breakdown in mental integration and result in perceptual disorders and irrationality. It was the discovery of antipsychotic properties in certain drugs which triggered off the whole recent development in psychopharmacology.

Psychotogenic drugs, on the other hand, are substances which will render an individual temporarily psychotic through the production of severe perceptual distortions and cause a fundamental interference with thought processes. Such psychotogenic drugs are capable of producing "model psychoses" in normal individuals, by causing a severe disturbance of integration in their mental apparatus. These model psychoses are reversible and last usually for a few hours.

Fig. 3 illustrates the effects of LSD-25, a highly potent psychotogenic drug, on the drawing performance of a woman volunteer, before and during the action of 125 gamma (γ) of the substance. Before administration of the drug, the subject drew the head of a horse. When she was asked to draw the same thing three hours after taking the drug, the disintegrating effect of this substance on the perceptual and psychomotor functions of the mental apparatus became evident. The whole configuration of the drawing is destroyed and the intention to express a specified concept can no longer be executed successfully.

Fig. 4 shows the opposite process at work, namely the re-integration of a psychotic individual under the effects of the antipsychotic drug, chlorpromazine. The first drawing was produced by a patient

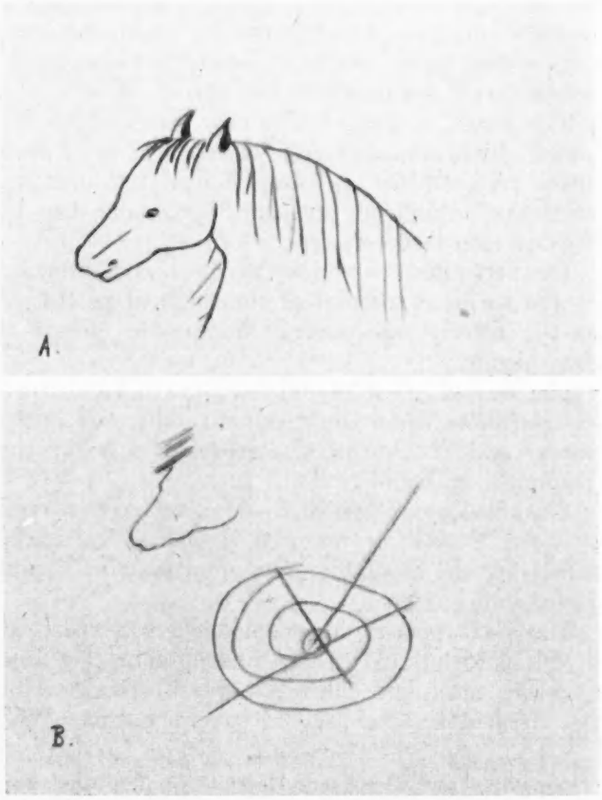

Fig. 3.—The effects of a psychotogenic drug as illustrated by two drawings made by a subject immediately before (A) and three hours after (B) the administration of 125 gamma of LSD-25.

during an acute catatonic attack, when he was requested to draw a house. The drawing obviously lacks integration although the patient clearly made an attempt to draw a house. There is only one empty window, no doors, no attempt at rendering perspective, and the roof is placed on the ground beside the house. Four days later, the same patient, who in the meantime had received chlorpromazine therapy, was again asked to draw a house. The result is the second drawing which is not very artistic but is as well integrated as a drawing of this subject by many normal people.

The drawings produced before and after the stimulant could be presented as the product of a sedative if they were reversed in order. Similarly, the drawings done before and after the sedative resemble those done after having received a stimulant, if the order of presentation of the drawings were reversed and the second drawing was presented as the first. In the same manner, the drawings illustrating the effects of antipsychotics and psychotogenic drugs could be interchanged, if the order of the drawings were reversed. This is, of course, due to the fact that these categories refer to the two extremes of the arousal and mental integration parameters respectively.

Finally, there is the mood parameter extending over the continuum from depression at one end to elation at the other. Only the mood at one end of the scale, depression, is attacked therapeutically by the use of psychotropic drugs of the antidepressant category. No drug is used systematically, either experimentally or therapeutically, to convert an elated mood into a depressed one. In this connection, reserpine, which is widely used as a hypotensive drug and also as an antipsychotic, produces depression in from 5% to 10% of cases. This undesirable property is a decided defect in this drug which is so valuable otherwise.

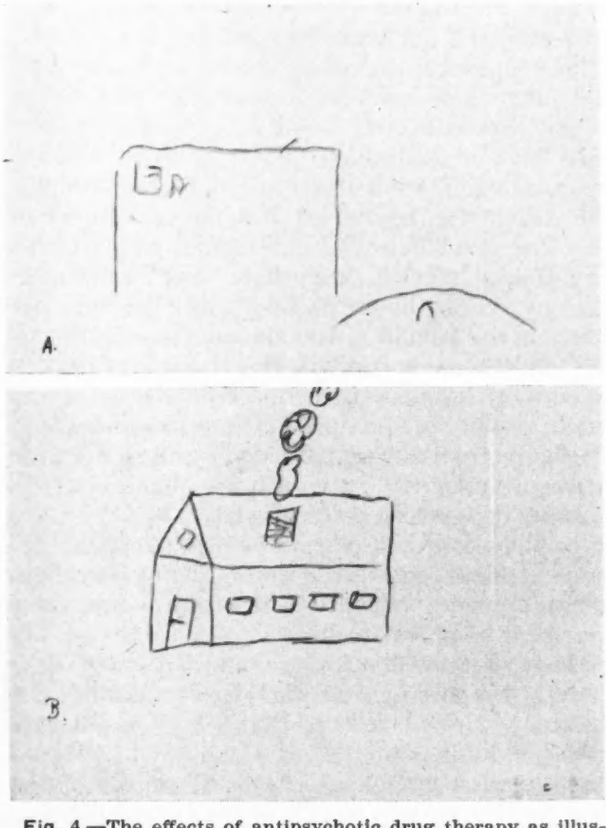

Fig. 4.—The effects of antipsychotic drug therapy as illustrated in two drawings by a patient during an acute attack of catatonic schizophrenia (A) and four days after (B) the start of treatment with chlorpromazine.

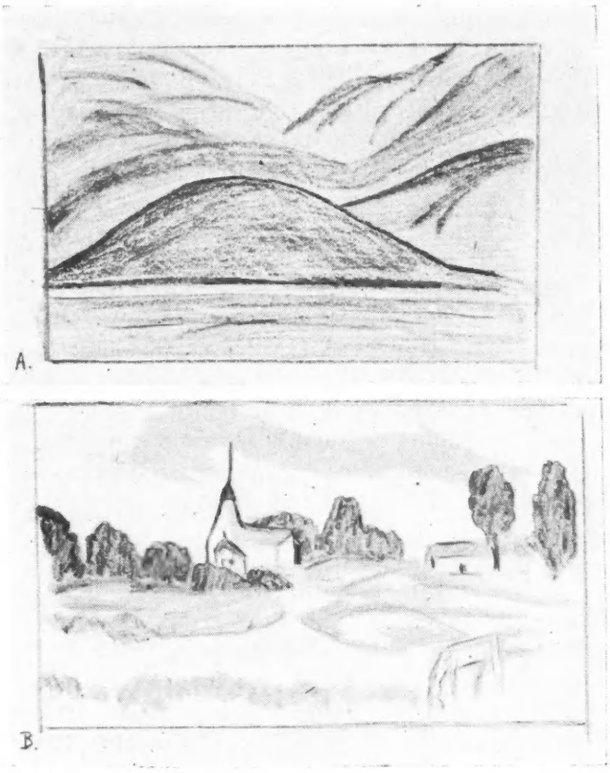

Fig. 5.—The effects of antidepressive therapy, as illustrated by two drawings made by a patient suffering from an endogenous depression (A) and four weeks later (B) after recovery from her depression.

The effects of an antidepressive agent are demonstrated in the next drawings (Fig. 5). The first picture was drawn by a woman suffering from a severe depression before treatment was started. She did the second drawing when she had completely recovered from her depression. These drawings illustrate better than words can that neither a change in arousal nor in mental integration was responsible for the final improvement; rather it is due to a complete reversal of feeling tone from a sombre and oppressive type of expression to a bright and animated one.

STIMULANTS; SEDATIVES; TRANQUILLIZERS

Among the stimulants most frequently used are caffeine, the amphetamines (e.g. Dexedrine), methylphenidate (Ritalin) and pipradol (Meratran). Stimulants have a relatively restricted field of application. They are specific for the treatment of narcolepsy and sometimes are useful in states of chronic lassitude, such as may be seen following a protracted disease, like certain virus infections. Some central stimulants, e.g., the amphetamines,

are helpful in programs of weight reduction, since the drugs tend to produce anorexia, probably through a direct effect on the hypothalamus. Although stimulants often produce euphoria as well as increased vigilance, these drugs play only a minor role in the treatment of depressive conditions. A severely depressed patient requires more than "just a lift and a boost". The therapeutic attack must be aimed at the mood parameter. If a depressed patient's arousal is increased by a stimulant and he is rendered more tense, he might also become more depressed. Stimulants are only occasionally effective in the treatment of depressions and then, as a rule, only when the depression is in its very beginning or already fading out. During a full-blown depression, stimulants should be avoided, since they might only increase the patient's anxiety.

There are two types of sedatives, those producing diffuse and those producing selective inhibition of cerebral functions. The older sedatives, such as barbiturates and chloral hydrate, exert their inhibiting effects on subcortical and cortical structures in the brain to an approximately equal extent; some of the newer tranquillizers, for instance those belonging to the phenothiazine group, affect the subcortical structures much more strongly than the cortex. As a result, inadequate doses of the older type of sedatives lead to uninhibited behaviour which manifests itself in increased restlessness; this is a pseudo-stimulation which appears as a release phenomenon when lower cerebral centres are no longer fully under the control of the cortex. The newer tranquillizers with their selective inhibiting effects on subcortical structures will not produce this disinhibition even when inadequate doses are given. Thus, the newer tranquillizers, for instance the phenothiazines, are particularly indicated in the symptomatic treatment of acute excitement, the result of a dissociation of cerebral control mechanisms. This is the case, for instance, in states of hysterical excitement. A patient in this state might become progressively more agitated, if barbiturates are given, until toxic doses have been reached and the patient slips into coma. Under these conditions, the newer tranquillizers are preferable because they will not produce disinhibition, even when inadequate doses are given.

PSYCHOTOGENIC DRUGS

There are three main representatives in the category of psychotogenic drugs: (1) mescaline, a substance derived from the Peytol cactus; (2) LSD-25 (lysergic acid diethylamide), which is an ergotamine derivative; and (3) psilocybine, a substance obtained from certain Mexican mushrooms. In addition, a number of other compounds with psychotogenic properties have been synthetically produced. At the present time this type of drug is used mainly for experimental purposes, in the study of the phenomena of artificially produced mental disorders and to investigate the accompanying physiological processes. However, in certain carefully selected cases, an experienced psychiatrist also may make therapeutic use of these drugs.

PHARMACOTHERAPY OF ANXIETY AND DEPRESSION

There are four principal conditions for which the non-psychiatric physician frequently requires the assistance of pharmacological agents. These four conditions are: (1) anxiety states, (2) depressions, (3) acute psychotic breakdowns, and (4) chronic psychotic conditions requiring maintenance therapy. It should be clearly understood that the treatment of anxiety states by drugs is only symptomatic at best. Not infrequently a patient manages to readjust himself and work through the stresses which produced the anxiety, if he is given temporary relief with sedatives. However, the treatment of choice in all anxiety states is still psychotherapy. If sedative drugs are given as supportive therapy in the treatment of anxiety states, the barbiturates and the minor tranquillizers ("minor" because they are not capable of suppressing specific psychotic symptoms), meprobamate (Equanil), chlordiazepoxide (Librium) and a number of others among the newer drugs, are more effective in reducing anxiety than the major tranquillizers or antipsychotic drugs, e.g. the phenothiazines or reserpine. The latter are less effective in anxiety states probably because they produce more unpleasant side effects than the barbiturates or the newer minor tranquillizers. On the other hand, any drug that reduces emotional tension and anxiety, without exacting a price in the form of unpleasant side effects, is a potential addiction hazard.

The physician who must treat a depression must determine first how threatening the condition is. Is the patient acutely suicidal? Does he refuse to take food or medication? Is he psychotic and uncooperative? These features may determine whether the patient can be treated at home or whether he requires immediate hospitalization; also whether he should receive immediate electroconvulsive therapy or can be treated with an antidepressive drug. If the patient is acutely suicidal, electroconvulsive treatment may be the therapy of choice, since most antidepressive drugs take from one to three weeks to produce definite improvement. Furthermore, a differential diagnosis must be made between endogenous and reactive depressions. In reactive depression, psychotherapy, either alone or in combination with other treatment, is often indicated; in endogenous depression, physical treatments are most effective, either electroconvulsive treatment or pharmacotherapy.

Once the decision to use antidepressive drug therapy has been made, the choice lies between the drugs which belong to the class of monoamine oxidase inhibitors and those which have no monoamine oxidase inhibiting effects. Examples of the first type are: iproniazid (Marsilid), phenelzine (Nardil), nialamide (Niamid), isocarboxazid (Marplan), tranylcypromine (Parnate), and

etryptamine acetate (Monase). Examples of the second group are: imipramine (Tofranil), amitriptyline (Elavil) and deanol (Deaner). Deanol is effective only in certain types of the milder depressions. Of the other antidepressant drugs, the monoamine oxidase inhibitors have about the same therapeutic effectiveness as imipramine and amitriptyline, which do not possess the enzyme inhibiting properties. About 60% of depressed patients show satisfactory improvement within three weeks when treated with any of the effective antidepressive drugs.

When prescribing a monoamine oxidase inhibitor the physician should remember that its effect is more far-reaching than the immediate drug action because the inhibition of monoamine oxidase is not easily reversed. This is the enzyme that destroys serotonin and noradrenaline; when these and other catecholamines are allowed to accumulate in its absence, various metabolic changes occur. The side effects and complications which are sometimes associated with the use of monoamine oxidase inhibitors do not as a rule disappear immediately when the drug is discontinued. The metabolic chain of events which is set in motion by the drug usually outlasts the pharmacological effect of the drug itself by considerable time. The patient receiving such drugs may develop a hypersensitivity to other substances such as novocaine or alcohol. There have been reports recently of dangerous reactions in patients who were receiving both a monoamine oxidase inhibitor and another antidepressant, imipramine, simultaneously. Drugs from both categories should not be combined. Furthermore, because of the prolonged after-effects of monoamine oxidase inhibiting drugs, at least a week or two should elapse before another antidepressive drug is given. On the other hand, imipramine or amitriptyline may be discontinued and monoamine oxidase inhibitor administered immediately, since the effect of the first two drugs will probably cease within a day or two of their discontinuance.

At the psychological level also, there is a difference in the action of the two types of antidepressants. The monoamine oxidase inhibitors tend to produce a state of mild euphoria which overcompensates for the depressed feeling; amitriptyline and imipramine exercise their effect mainly by eliminating the symptoms of depression without bringing about a change of mood in the opposite direction. However, any antidepressive drug, and for that matter, electroconvulsive therapy as well, may convert an endogenous depression into a manic episode in those patients who are predisposed to such swings in psychopathology. Since none of the antidepressive drugs available so far can do more than suppress the symptoms of a depression, it is essential to continue maintenance therapy for at least a month and sometimes for much longer after improvement has taken place.

PHARMACOTHERAPY OF PSYCHOTIC CONDITIONS

Acute psychotic episodes now frequently improve within a few days with the use of the new antipsychotic drugs; these states previously lasted for months and even with shock therapy required weeks for a successful resolution of symptoms. The prototype of the antipsychotic agents is chlorpromazine (Largactil, Thorazine); it was discovered first and still serves as the standard against which newer drugs are evaluated. Chlorpromazine is a phenothiazine derivative and so are most of the antipsychotic drugs on the market. However, there are other chemical compounds which have similar pharmacological and therapeutic properties although their structural formula does not resemble that of the phenothiazine derivatives. The effectiveness of reserpine as an antipsychotic was discovered at about the same time as chlorpromazine; however, this drug has certain drawbacks. The delay in the onset of its therapeutic effect is longer than that of the phenothiazines; some of its side effects are more difficult to manage than those of other antipsychotics; and it is somewhat less reliable in its action. Recently two new pharmacological agents with antipsychotic activity, which are not phenothiazine or reserpine derivatives, have been developed: the thioxanthenes (e.g. Tarasan) and the butyrophenones (e.g. Haloperidol).

The antipsychotic drugs may be roughly divided into two groups: (1) those with side effects manifesting themselves mainly in disturbances in autonomic functions (hypotension, miosis, tachycardia, dry mouth, excessive perspiration and other symptoms of adrenergic-cholinergic dysbalance), and (2) those with side effects expressed mainly in the extrapyramidal system (parkinsonism, muscular dystonia, etc.). If the drug is a phenothiazine derivative, the nature of its side effects can usually be predicted from the type of side chain attached to the phenothiazine nucleus. Drugs with a piperazine ring in the side chain are usually much more potent, milligram for milligram, and much more likely to produce extrapyramidal symptoms than drugs with an aliphatic side chain. The latter are more likely to produce changes in autonomic functions and must be given in higher doses.

Antipsychotic drugs are not always tranquillizers. Some of them have distinctly stimulating effects and may produce increased tension and anxiety because of the akathisia which they produce; this is an extrapyramidal symptom manifesting itself in disturbing restlessness and the inability to sit still. These extrapyramidal side effects, either hypokinetic parkinsonism or hyperkinetic akathisia, may be so disturbing that anti-parkinsonism drugs must be employed to counteract these symptoms. The agents most frequently used for this purpose are: trihexyphenidyl hydrochloride (Artane), benztropine methylsulfonate (Cogentin), and procyclidine hydrochloride (Kemadrin). Many psychiatrists believe that the development

of extrapyramidal symptoms is necessary before the therapeutic effect of these drugs is obtained, but there is insufficient evidence to support this claim. Some antipsychotic drugs such as chlorpromazine (Largactil) and levomepromazine (Nozinan) have distinct tranquillizing or sedative properties. They offer definite advantages when the psychotic patient is agitated, as in acute manic or catatonic excitement. Other drugs with no sedative effect may be more desirable in the treatment of psychotic conditions such as certain passive schizophrenic states where further sedation would be contraindicated.

Phenothiazine derivatives with a piperazine ring in the side chain: prochlorperazine (Stemetil, Compazine)); perphenazine (Trilafon); thiopropazate (Dartal); trifluperazine (Stelazine); fluphenazine (Prolixin); thioproperazine (Majeptil).

Phenothiazine derivatives with a piperidine ring in the side chain: mepazine (Pacatal); thioridazine (Mellaril).

Of these drugs, thioproperazine produces extrapyramidal symptoms most frequently and thioridazine least frequently.

TABLE I.—SIDE EFFECTS AND COMPLICATIONS OF PSYCHOTROPIC DRUGS

	Common	*Uncommon*	*Rare*
1. Psychiatric	Somnolence, apathy, restlessness	Depression, anxiety, toxic psychosis	
2. Neurological	Extrapyramidal symptoms, parkinsonism, akathisia. Syncope	Convulsions, loss of muscular tone	
3. Autonomic	Dryness of mucous membranes, hypotension, excess perspiration, tachycardia		
4. Dermatological	Photosensitization	Skin rashes, edema	
5. Endocrine	Obesity. Menstrual irregularity		Galactorrhea
6. Metabolic		Cholestatic jaundice	Hepatic necrosis
7. Urologic		Retention of urine	
8. Ophthalmological	Disturbance of accommodation, miosis		Ulceration of cornea, pigmentation of retina
9. Gastrointestinal	Constipation		Ileus, perforating ulcer
10. Hematological		Leukopenia	Agranulocytosis

Although most antipsychotic drugs have a remarkably low toxicity and an extraordinarily wide therapeutic margin, they also have an unusually broad range of unpleasant side effects. This is probably why, in thousands of cases treated with antipsychotic drugs, many psychiatrists have never seen a single case of true addiction. Table I shows the great range of side effects and complications that may be encountered during therapy with tranquillizers and antidepressants; it also shows the relative frequency of these phenomena.

In the following paragraph, a list of currently used phenothiazine derivatives is given. This list is not complete and no attempt is made to state specific dosages or indications for each drug. The dosages can best be obtained from the information provided by the manufacturer. As for *specific* indications for each member of the various groups, there is some doubt that these really exist. The drugs differ in the dosage required, the frequency, and type of side effects produced; but the same overall therapeutic effect can be obtained with any one of the various potent antipsychotics now available. Systematic clinical trials carried out with double-blind controls have failed to show significant differences in therapeutic effectiveness of different antipsychotics; there were a few exceptions in those drugs whose limited usefulness was known empirically before the experiments.

Phenothiazine derivatives with a di-methyl structure in the side chain: chlorpromazine (Largactil, Thorazine); triflupromazine (Vesprin); levomepromazine (Nozinan); promazine (Sparine).

Almost any of the phenothiazine derivatives that have antipsychotic properties will give equally good results in the hands of a physician who knows the proper indication, dosage and timing for the drug. Consequently it is of the greatest importance for him to gain experience with one or two of these drugs over a long time and under varied conditions. The advantages gained by having experience with one older drug probably outweigh the potential advantages of prescribing a new one with slightly different side effects but with similar effectiveness. An acute psychotic condition is preferably treated with intramuscular injections of the drug chosen, at least for the first few days; then a change to oral administration can be instituted. Acute psychotic states usually require rather high doses. The risk of giving too much of these new drugs is small if the general framework of the recommended dosage is followed and one or two test doses are given to observe the patient's general reaction to the drug.

Chronic psychotic conditions frequently require maintenance therapy with an antipsychotic drug for many months and sometimes for years. The maintenance dose is usually from one-sixth to one-fourth of the dose necessary in the treatment of the acute condition. If maintenance therapy is interrupted the risk of a relapse is considerable; this happens frequently because the patient wants to discontinue his medication. Reports from several independent authorities indicate that psychotic patients have a relapse rate of 30%-50%; this can be reduced to 10% or 15% provided the patient remains on regular follow-up therapy. At times of

increased stress, family conflicts, job changes, and during similar problems, the maintenance medication may be increased for a short time; this also applies if the patient begins to show signs of increasing tension or instability. The therapeutic situation is similar to that of an epileptic patient on anticonvulsant therapy or of a diabetic on insulin, i.e., the treatment is neither directed to the control of symptoms alone nor curative, but corrective or compensating.

In the past, before the era of antibiotics, a physician who was restricted to the use of only two drugs in his practice might most profitably have chosen morphine and digitalis. The physician of today would probably select penicillin as the third drug in his therapeutic emergency supply. There is now good reason to make one of the major tranquillizers with antipsychotic properties the fourth drug; at this time, chlorpromazine would still be the best choice. We may hope that a fifth drug, the prototype of antineoplastic agents, may soon be added to our therapeutic treasury.

SUMMARY

Psychotropic drugs are those agents which have a direct influence on behaviour, perception, mood or thought processes. They are considered under five principal categories which in turn refer to three basic parameters of psychological functioning. These three parameters are: (1) arousal; (2) mental integration; (3) mood. From their extremes, the categories of stimulants and sedatives; of drugs with antipsychotic or psychotogenic effects; and finally, drugs with antianxiety or antidepressive action, i.e. tranquillizers or antidepressants, can be distinguished.

Stimulants are not necessarily effective in depressions; they often increase anxiety. Sedatives may produce either diffuse or selective inhibition of cerebral functions. The older sedatives such as the barbiturates bring about marked cortical as well as subcortical inhibition; consequently during some phases of their action they may produce disinhibited behaviour as a release phenomenon. The newer tranquillizers do not produce such disinhibition.

Experimentally, psychotogenic drugs can produce states of psychotic disintegration. Antipsychotic drugs are substances which have a therapeutic effect on symptoms of a specifically psychotic nature, such as hallucinations or autistic thought disorder. Antidepressants may be divided into drugs with monoamine oxidase inhibiting activity and those without such characteristics.

The four principal conditions in which the nonpsychiatric physician most frequently requires the assistance of pharmacological agents are: anxiety states, depressions, acute psychotic breakdowns and chronic psychotic conditions.

The treatment of anxiety states by drugs is at best only symptomatic; psychotherapy is usually required for this condition and also in the treatment of reactive depressions, although pharmacotherapy may serve as a powerful aid. On the other hand, drugs have become almost indispensable in the therapeutic management of psychotic conditions, both acute and chronic.

Indications for drug therapy in psychiatric conditions should be based on clear diagnosis; on complete information regarding the pharmacological properties of the drug to be prescribed; and on a careful evaluation of these factors combined, with a view to possible side effects of the drug. It is important to gain experience with one or two drugs in each category over a long time and under varied clinical conditions.

CANADIAN JOURNAL OF SURGERY

Volume 4, No. 5 issue of the Canadian Journal of Surgery, published in October 1961, contains the following original articles, case reports and experimental surgery:

Original Articles: Etude clinique de 238 cas d'endométriose chirurgicale—B. Lambert, P. Meunier et C. Ouiment. The problem of late local recurrence of carcinoma of the cervix—J. P. A. Latour and W. D. Fraser. Hypertensive reaction following resection of coarctation of the aorta—R. K. Padhi, E. M. Nanson and R. B. Lynn. Surgical experience in resection of aneurysms of the thoracic aorta—P. Allen, R. Robertson, W. G. Trapp and W. A. Dodds. Thoracic sequestration cysts of fetal bronchogenic and esophageal origin—G. B. Elliott, G. E. Miller R. H. Walker and K. A. Elliott. Nitrogen mustard in treatment of metastatic carcinoma of the testis—G. J. Ankenman and J. Balfour. Epithélioma colloïde du sein—R. Tremblay et J.-L. Bonenfant. Preauricular sinus—J. A. McLachlin and R. O. Farley. Primary basilar impression of the skull—H. F. W. Pribram and R. J. Porter.

Case Reports: Splenic aneurysm—R. E. Pow, G. B. Elliott and B. Freigang. Two synchronous primary malignant tumours (kidney and colon)—T. S. Wilson. Mesenchymoma in the retropubic space—C. Schneiderman, M. A. Simon and M. M. Gelfand. Thymic cysts of the neck—R. Coté and C. Fortin. Rupture of aortic aneurysm into duodenum: a successfully treated case—W. A. Maclean and C. M. Couves.

Experimental Surgery: The etiology and pathogenesis of cholecystitis: an experimental study—D. J. Currie. Some observations on peripheral blood flow, blood gas, and electrolyte content of the dog's limb after sympathectomy—R. K. Padhi and R. B. Lynn. Splenic and bone marrow homografts in the dog after lethal body irradiation—J. W. Irvine and S. Kling.

Subscription rates to the Canadian Journal of Surgery are $10.00 per year for four issues or $2.50 for a single copy.

Canad. M. A. J.
Nov. 18, 1961, vol. 85

CASE REPORT

MOLLUSCUM CONTAGIOSUM VENEREUM

E. SNELL, L.R.C.P.(Edin.), D.P.H.* and
J. G. FOX, M.D., Cert. Path.,† *Winnipeg, Man.*

NO REFERENCE to molluscum contagiosum can be found in the Canadian medical literature of the past twenty years. Nevertheless, the disease is not unknown, since the pathologist[1] of a large general hospital in Winnipeg has reported nine biopsy specimens as molluscum contagiosum in the past nine years.

White and Robey,[2] writing in 1902, give a very comprehensive review of the literature up to that date, and attribute the original description of the disease to Bateman; it is contained in a book written in 1817. Until 1910 the disease was believed to be limited to the British Isles. Walker[3] states, "This disease appears to be entirely British, no case of it having as yet been recorded, insofar as we are at present acquainted, in the records of any other country"; he was the first to attribute its spread to the use of public baths. However, by 1915 cases were being reported[4] from the continent of Europe; and the disease is now known to be world-wide in distribution. Before the Second World War, Low[5] diagnosed about two cases of molluscum contagiosum in every thousand patients he saw at the skin department of the Edinburgh Royal Infirmary; during the war, there were about half as many. It is not improbable that the incidence in Manitoba is of the same order of magnitude.

The disease is mainly seen by dermatologists, pediatricians and ophthalmologists but a number of cases have been reported in which the condition seems to be venereal in origin.[4, 6-9] The present case is of this nature and is recorded to help to establish molluscum contagiosum venereum as a definite clinical entity.

The disease has numerous synonyms, and Ormsby and Montgomery[6] list the following: molluscum sebaceum, epithelioma contagiosum, molluscum epithiale, and acne varioliforme (Bazin). An excellent description of the clinical appearance of the lesion is given by Pillsbury, Shelley and Kligman,[10] who state that the small typical lesion can hardly be mistaken for anything else. It is a slightly bulbous, sessile papule, the surface of which is umbilicated. The normal colour is yellow to pink. The usual diameter of the lesion is between 2 and 5 mm. but lesions of much larger size, up to 1.5 cm. or more, have been reported. Long-standing lesions sometimes become inflammatory at the base and may resemble furuncles, presumably because of secondary bacterial infection. The lesions are most frequently seen on the trunk, face and anogenital region, and occur most frequently in children; there are occasional epidemics in schools or institutions. Pediatric cases have been described by Votteler,[11] Mopper,[12] Niedelman,[13] Vollmer[14] and others. In all of these cases short courses of treatment with one of the tetracycline drugs was successful; in children this method of treatment is favoured because of its ease of administration and lack of trauma. Sommerville[16] records the successful treatment of six out of eight cases with sulfapyridine; he was encouraged to use the drug because of the success achieved in the treatment of secondary infection in molluscum contagiosum in a boy aged 15 years. Laymon[17] later reported the cure of a child aged 12 with sulfadiazine. In adults, antibacterial treatment has not been so successful. Hill and Downing[18] reported partial response of a 44-year-old man to sulfapyridine but curettage of a residual lesion was necessary in this case. Guy, Jacob and Guy[19] reported successful treatment with chlortetracycline, but the age of their patient was not given. Hill and Messina[20] reported two adults with molluscum contagiosum of the scalp in which sulfapyridine and podophyllum resin were unsuccessful but a cure was eventually achieved with excision and electrodesiccation.

Molluscum lesions not uncommonly affect the eyelid[21] and in this location they are often difficult to diagnose; they cause such complications as conjunctivitis and keratitis. Cases of this nature have been described by numerous authors.[22-25] In all of these cases, cure of the lesion and the complications associated with it was obtained by surgical removal or curettage.

An unusual case of molluscum contagiosum affecting the mucous membrane of the lower lip was described by Schiff;[26] the lesion was cured when it was removed during the biopsy as a possible cyst.

In 1915 the suggestion of a possible venereal etiology of this lesion first was made by McLeod[4] in describing the case of a navy serviceman, 40 years of age; this man had numerous lesions on the inner surface of the thighs, groins, pubes, scrotum and penis. McLeod wrote that although molluscum contagiosum affecting the genitalia was very rare in Britain, it was said to be very common on the Continent. Ormsby and Montgomery[6] mentioned that patients sometimes mistake lesions on the genitalia for some form of venereal disease. Gudgel,[7] in discussing the question of a venereal etiology for this disease, reported that he had observed many cases of molluscum contagiosum exclusively located on the genitalia of young soldiers, the majority of whom had had repeated intercourse with Korean prostitutes. He concluded

*Director, Bureau of Venereal Disease Control, Department of Health and Public Welfare, Manitoba, and Consultant Venereologist, St. Boniface General Hospital.
†Pathologist, Provincial Laboratory, Winnipeg, Man.

that using the definition of venereal literally, "due to or propagated by sexual intercourse", it must be considered that this is indeed a venereal disease in these cases. Many of Gudgel's patients had not noticed the lesions for months after their last exposure in Korea and if specific enquiry had not been made, the venereal nature of the disease might have been overlooked. Treatment was that of desiccation and curettage. Gordon and Stearns[8] reported a patient with this lesion who had a history of sexual contact six weeks earlier; he had developed discomfort and bleeding of the penis immediately thereafter. This patient was treated by various physicians for what was believed to be a dermatitis, with a moderately satisfactory response. However, a number of vesicles persisted and these were treated with tetracycline. This medication did not affect the vesicles which, for the first time, were noted to have a central depression. Dermatological consultation suggested the possibility of molluscum contagiosum, and the diagnosis was confirmed by biopsy. The lesions were electrodesiccated under local anesthesia and healed well with no recurrence. Mitchell[9] reported the result of investigations on the sera of a total of 14 patients with molluscum contagiosum; of these, three had a heavy infection of the genital region. Only these three patients had sera which gave positive complement fixation with the molluscum antigen.

ETIOLOGY

The agent is an epithelial-trophic virus grouped with the "pox viruses". There are no reliable serological procedures to establish the diagnosis; this is made in the usual case by examining a paraffin-sectioned biopsy with light microscopy. The virus has not been successfully isolated or grown *in vitro*, but Seitz filtrates from ground-up lesions are infective. Man is the only known host. The cytopathogenic effects such as the presence of elementary bodies seen in human biopsy material are characteristic of viral lesions.

GROSS MORPHOLOGY

Generally, the lesions of molluscum contagiosum are papillary, under 1 cm. in diameter, centrally umbilicated, round in outline and pink and waxy in appearance. They may occur singly but are generally multiple and discrete.

MICROSCOPIC PATHOLOGY

A bulbous epithelial downgrowth is characteristic; this epithelial lobulation is almost diagnostic. Molluscum bodies are generally seen but may be absent; they are homogeneously staining eosinophilic cells originating in the deeper epidermal layers and often form centrally located nests in lobulated epithelial downgrowths. The nuclei are inconspicuous and the molluscum body is likened to an operculum containing huge numbers of elementary bodies in a mucoid matrix. Secondary infection is common and may result in a leukocytic infiltrate in the surrounding dermis. The fully developed molluscum bodies are usually located centrally in the superficial layers of a loculated lesion.

Molluscum bodies range from 20-30 μ in diameter while the elementary bodies, as revealed by electron microscopy, are brick-shaped and have an average diameter of 200-300 μ.

CASE REPORT

M.L., a 25-year-old Portuguese male, attended the government Venereal Disease Clinic at St. Boniface General Hospital for the first time on April 27, 1961. This man had arrived in Canada one month earlier. He had not suffered any serious ill health previously but had been given a short course of penicillin about two years before for minor boils. This medication had caused no untoward effects.

He admitted sexual contact with a white female eight weeks earlier in the Azores, but before that had not had intercourse for many months. Two weeks after this contact he developed a crop of lesions on the skin of the groin on both sides, which were itchy and a little painful. They all developed simultaneously. Otherwise he had not felt ill and there had been no noticeable headache, pyrexia or any other general symptoms. The lesions had gradually increased in size, and about a week prior to his clinic attendance he noticed a bluish swelling in his left inguinal region.

On examination, he had about a dozen lesions on the groin on each side, which consisted of definitely raised papules about 5 mm. in diameter. They were a waxy pink in colour and on palpation felt quite solid and rubbery. There was no tenderness except over an area in the left groin where there was a fairly large semifluctuant swelling with purplish induration of the overlying skin. The patient returned on May 1 for biopsy and was given tetracycline 250 mg. every six hours. In the meantime, serological tests for syphilis were reported as negative.

Tissue Pathology

In the gross the specimen was a small skin biopsy measuring 1 cm. in length by 0.5 cm. in breadth which contained underlying dermis to a depth of 0.4 cm. In the centre of the skin surface was a well-circumscribed nodular lesion 0.3 cm. in diameter and raised to a height of 0.2 cm. The lesion was waxy in appearance, had a slight pinkish hue and was centrally umbilicated.

On microscopic examination the section consisted of a minute ellipse of epidermis, 1 cm. in length with underlying dermis to a depth of 0.3 cm. In the centre of the ellipse but deep to the epidermis, by several micra, was a lobulated, centrally cystic, epithelial structure, containing many deep-staining eosinophilic bodies. The central superficial bodies had a homogeneous structure while the deeper ones showed a more granular trabeculated appearance. The more basal epithelial cells had a columnar and pallisaded arrangement; the superficial layers of the epithelial downgrowths contained much blue-staining pigmented material (H.P.S. stain). Some of the molluscum bodies stained a greenish-blue to brown colour. Several of the deep lobules were centrally cystic and resembled small epi-

Fig. 1(a)

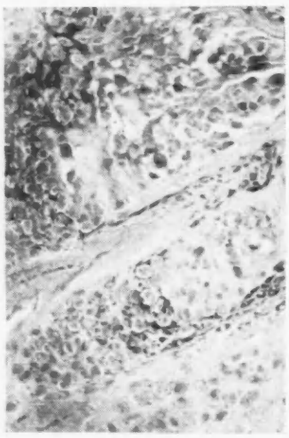

Fig. 1(b)

Fig. 1(a).—The lesion seen with scanning lens showing trabeculated bulbous epithelial downgrowths and centrally located clusters of molluscum bodies. **Fig. 1(b).**—The lesion seen under high dry lens showing molluscum bodies and marked pigment deposits.

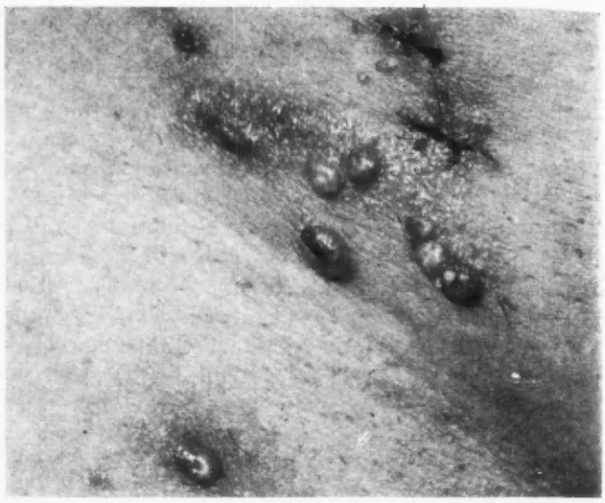

Fig. 2.—Molluscum contagiosum venereum. The typical appearance of the lesions can be seen; the umbilication or central depression is well marked in the solitary lesion in the lower part of the figure.

dermal cysts, while other downgrowths were centrally stuffed by molluscum bodies and keratinous material. The pathological diagnosis was molluscum contagiosum.

Three days later the lesions showed no improvement except that the area from which the biopsy had been taken was healing satisfactorily. On further examination two or three of the lesions on each side showed quite definite umbilication or central depression; in these there appeared to be a thick, whitish, cheesy material which could not be easily expressed (Fig. 2). The dosage of tetracycline was increased to 500 mg. every six hours and this was continued for four more days. This treatment produced no apparent effect; in fact, when next seen on May 11, the abscess on his left groin was larger and more fluctuant.

All the lesions on the right side were removed with a sharpened sterile wooden applicator without anesthesia. They shelled out with surprising ease, and the patient complained of no pain. Some scratch marks were noticed over the region where the hair had been shaved. Therapy with tetracycline was continued in the increased dosage for another four days. Then, because there was still no sign of improvement in the lesions on the left, they were removed with the applicator also and the bases were dabbed with liquor iodi mitis. On the right side where the lesions had been removed earlier there were now only some scabbed areas, and healing appeared to be taking place. The dosage of tetracycline was now reduced to the original level. By May 18 he was feeling well and had started to work on the railway, and the lesions continued to heal. There was still evidence of secondary infection in the left inguinal region and the antibiotic was continued for one more week. By May 25 healing was well advanced. All treatment was discontinued.

SUMMARY

A short description of molluscum contagiosum is given; this disease chiefly affects children, but in adults it involves the skin of the face, trunk and anogenital region. Lesions of the eyelid are difficult to diagnose, and cause secondary conjunctivitis and keratitis. Although this disease is usually spread by direct contact or through fomites, a number of cases have been reported in which it appears to have been spread during the intimate contact of sexual intercourse. Thus the disease can be classified among the venereal infections. From a perusal of the literature, treatment with sulfonamides and broad-spectrum antibiotics appears to have been successful mainly in pediatric cases. Electrodesiccation or extirpation of the lesions is curative. A case has been described in which a venereal mode of spread was strongly suggested both by the history and by the location of the lesions. Treatment with tetracycline over a prolonged period was unsuccessful; but the shelling out of the individual lesions with a sharpened sterile wooden applicator was accomplished without pain or anesthesia and resulted in cure. It is considered that cases of this type should be described as molluscum contagiosum venereum.

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SHORT COMMUNICATION

WHEN IS THE APPENDIX NORMAL?
A STUDY OF ACUTE INFLAMMATIONS OF THE APPENDIX APPARENT ONLY UPON HISTOLOGIC EXAMINATION*

J. S. CAMPBELL, M.D.,
PIERRE FOURNIER, M.D. and
T. DASILVA, M.D., *Ottawa, Ont.*

WHILE "acute focal" inflammation has been observed in appendices removed from patients in whom a clinical diagnosis of acute appendicitis was established preoperatively, the same lesion has been discovered only somewhat less frequently in histologic examinations of appendices incidentally removed.[1] Furthermore, acute appendicitis with mucosal ulceration or with involvement of muscular or serosal coats has been observed as an incidental finding.[2] Thus casual correlations of the clinically "acute abdomen" to minor appendicular inflammatory lesions are open to doubt. In the following survey, various histologically apparent, acute inflammatory lesions of the appendix were considered to be subclinical because there was no record of abdominal symptoms and signs or of operative findings to support a diagnosis of acute appendicitis, and "hyperacuity" on the part of the laboratory observers seemed to be responsible for the perhaps unduly frequent reporting of clinically insignificant appendicular inflammations.

MATERIALS AND METHODS

Surgical pathology reports of 1000 consecutive appendectomies performed from January 1957 to the end of April 1958 in five hospitals served by this pathology department were reviewed (Table I).

TABLE I.—INCIDENCE OF MINOR APPENDICULAR INFLAMMATIONS IN 1000 CONSECUTIVE APPENDECTOMIES, JANUARY 1957 TO APRIL 1958

Total operations (16 months)	6693
Total appendectomies	1000
Primary appendectomies	578
Superficial appendicular inflammations in primary appendectomy (6.2%)	36
Incidental appendectomies	422
Superficial appendicular inflammations in incidental appendectomy (6.6%)	28
Incidental appendicular inflammations unassociated with acute right lower quadrant abdominal pain (4.0%)	17

Three sections of each appendix were examined histologically, the proximal and middle thirds in transverse section and the distal third in longitudinal section. Acute inflammations were designated as "focal" when only one segment of the appendix was involved; as "extensive" when more than one segment was involved; as "superficial" when neutrophilic polymorphonuclear leukocytic infiltration was limited to the surface or glandular epithelium and to the submucosa; and as "diffuse" when the muscularis and serosa were involved. Minimal pathologic criteria for a diagnosis of acute appendicitis were neutrophilic polymorphonuclear leukocytic infiltrations superficially in the mucosa with, or infrequently without, neutrophilic polymorphonuclear leukocytes in the lumen (Fig. 1).

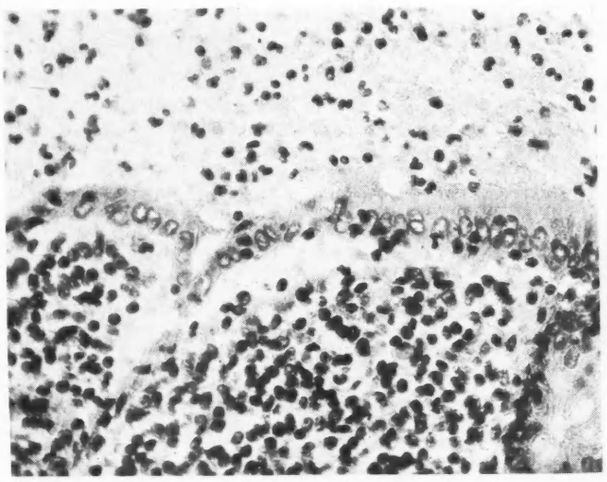

Fig. 1.—The inflammatory reaction here provides what, in this study, were considered minimal criteria for the diagnosis of acute focal appendicitis. The subepithelial clear zone may be due to edema rather than artefact and thus represent a pre-ulcerative focus (hematoxylin, phloxine and saffron, × 350).

A particular object in the histologic examination of appendices removed during 1960 was to detect evidence of superficial inflammations. The incidence of these lesions in appendices removed incidentally was obtained from diagnostic cross index references to appendectomies performed in the Ottawa General Hospital. The incidence of similar lesions in appendices removed because of acute abdominal symptoms was recorded in records of the Medical Audit and Tissue Committee of the Ottawa General Hospital.[3] During 1960 the technique for preparing sections, the histologic criteria and the observers responsible for diagnosis were the same as in 1957 and 1958.

RESULTS

Among 422 appendices removed incidentally from January 1957 to April 1958 there were 28 that showed acute inflammation. Excluded from detailed study were 10 cases in which clinical diagnoses were acute mesenteric adenitis and one case in which appendectomy was performed upon an individual thought to suffer from recurrent bouts of appendicitis. The clinical records and tissue

*From the Departments of Pathology and Surgery, University of Ottawa, Faculty of Medicine, and Ottawa General Hospital, Ottawa, Ont.

TABLE II.—VARIETIES OF INCIDENTALLY OBSERVED MINOR APPENDICULAR INFLAMMATIONS AND ACCOMPANYING LESIONS OF THE APPENDIX IN 1957 AND 1958 SURVEY

Appendicitis	*No. of patients*
Acute superficial, extensive	7
Acute superficial, focal	4
Acute ulcerative, focal and superficial	4
Diverticulitis of the appendix	2
Accompanying lesions	
Fibrosis	6
Stasis of feces	3
Carcinoid	1
Endometriosis	1
Enterobius infestation	1
Periappendiceal adhesions	1
Fecaliths	0

sections of the remaining 17 cases were reviewed (Tables II-IV).

All of the acute appendicular inflammations reviewed in Table II were superficial. In two cases superficial leukocytic infiltrates were limited to diverticula at the tips of the appendices (appendicular diverticulitis). Four appendices contained focal ulcerations. In one such instance, extensive but superficial appendicitis with mucosal ulcerations in the tip (Fig. 2) was observed in a 54-year-old woman whose appendectomy was incidental to cholecystectomy for cholelithiasis and chronic cholecystitis. This patient's chief complaint was recurrent epigastric pain, but diffuse tenderness to palpation was encountered in the right upper and right lower abdominal quadrants. There was no muscle guarding or rebound pain. The leukocyte count was 7500/c.mm. The cecum and appendix occupied the usual right lower abdominal position. The abundance of histiocytes in the lumen and the presence of lymphocytes and eosinophilic polymorphonuclear leukocytes in the muscularis and serosa of the superficially ulcerated tip were consistent with resolving rather than with incipient inflammation. None of these appendices contained fecaliths.

Fig. 2.—Acute focally ulcerative appendicitis. Here is the most severe grade of incidentally observed appendicitis that was encountered in our survey (hematoxylin, phloxine and saffron, × 55).

TABLE III.—AGE, SEX AND EXTRA-APPENDICULAR DISEASE ACCOMPANYING INCIDENTALLY OBSERVED MINOR APPENDICULAR INFLAMMATIONS IN 1957 - 1958 SURVEY

Females	13	Age: Mean	34
Males	4	Range	6 - 74 years

Diagnoses	*No. of patients*
Chronic cholecystitis, cholelithiasis	3
Leiomyomata uteri	3
Ovarian cyst (dermoid, adenofibrocystoma)	2
Hemorrhage from ovarian cyst	1
Hemorrhagic corpus luteum	1
Hydrosalpinx, right	1
Pelvic endometriosis	1
Uterine retroversion	1
Visceroptosis (psychoneurosis)	1
Peptic ulcer of stomach (tension syndrome)	1
Inguinal hernia	1
Shigellosis	1

TABLE IV.—SYMPTOMS AND SIGNS OF INTRA-ABDOMINAL DISEASE IN 17 CASES OF INCIDENTALLY OBSERVED MINOR APPENDICULAR INFLAMMATIONS, 1957 AND 1958

	No. of patients
Abdominal pain	13
Chronic or recurrent lower quadrant abdominal pain	7
Chronic or recurrent lower abdominal pain limited to right lower quadrant	1
Acute abdominal pain	*1
Acute abdominal pain limited to right lower quadrant	0
No abdominal pain	4
Abdominal tenderness	8
Abdominal tenderness limited to right lower quadrant	2
Abdominal muscle guarding and peritoneal rebound pain	0
Negative physical findings	9
Leukocyte count:	
Mean 7300/c.mm. Range 3400 - 10,200/c.mm.	14
In excess of 10,000 w.b.c./c.mm. (64% polymorphonuclear leukocytes)	1
Diagnoses of appendicitis established preoperatively or at laparotomy	0

*1 - 2 hour duration, radiating to vulva and legs.

In 1957 and early in 1958 superficial appendicular inflammation was found in 6.2% of all primary appendectomies and in 6.6% of all incidental appendectomies (Table I). In 1960 superficial appendicular inflammations were more frequently reported (Table V). Here, in the case of every primary appendectomy it was assumed that acute diffuse appendicitis was responsible whenever the patient sought medical attention for symptoms which led to operation. The 76 instances of diffuse appendicitis were subtracted from the total of 141 primary appendectomies; in 27, or about 40% of the remaining 65 cases, superficial appendicular inflammations were found. The same lesion was present in 24, or about 35%, of 68 appendices removed *en passant* during 1960. Therefore, on microscopic examination superficial appendicular

TABLE V.—INCIDENCE OF MINOR APPENDICULAR INFLAMMATIONS IN 1960 SURVEY

	No. of patients
Primary appendectomies (June - December)	141
Acute diffuse appendicitis	76
Superficial appendicular inflammation	27
No inflammation	38
Incidental appendectomies (January - December)	68
Superficial appendicular inflammation	24
No inflammation	44

inflammations were found almost as often in incidentally removed appendices as in primarily removed appendices in which no diffuse inflammatory changes were present to explain acute abdominal symptoms. The number of superficial appendicular inflammations recorded in 1960 was about 7 to 9 times greater than that reported by the same observers at an earlier period.

COMMENT

Schenken, Anderson and Coleman[1] correlated the clinical signs and symptoms of acute appendicitis with lesions designated as acute focal appendicitis, found in 32.5% of 2750 surgically removed appendices. Acute focal appendicitis, however, was found in 24.2% of 649 incidentally removed appendices included in Schenken's study. These lesions were characterized by "purulent material in the lumen without demonstrable exudate in the mucosa or wall of the appendix". Utilizing criteria more exclusive than these, an even greater incidence of comparable minor appendicular inflammations has been recorded. In our study, superficial appendicular inflammations were almost as common in incidentally removed appendices as in a group of primarily removed appendices without diffuse appendicitis; in many of the latter, therefore, an extra-appendiceal source for the acute symptoms leading to laparotomy could be suspected.

Other workers have reported acute appendicitis in 2-12% of incidentally removed appendices.[2] So variable an incidence may be attributable to differences in the criteria for the diagnosis of minimal grades of appendicitis; but in our study, to account for a ninefold increase in the reporting of acute appendicitis as an incidental finding, diagnoses of acute appendicitis during 1960 must often have been made when clinically unimportant inflammatory exudates were detected by microscopic examination of appendices. At least, the minor appendicular inflammations we reported so frequently during 1960 were regarded by some as artefacts of histologic interpretation, and we were reproached for adding to the iatrogenic diseases produced in the laboratory. Other explanations, however, are not wholly implausible. In one view, appendices may be regarded as congenital diverticula subjected by reason of their considerable length and narrow lumina, to degrees of stasis that are so predisposing to bouts of inflammation that acute appendicitis, incidental or otherwise, is, as would be expected, commonplace. Thus the ubiquitous fibrosis of the appendix may result from episodes of superficial inflammation rather than from simple involution of lymphoid tissue. Such a view is not in conflict with classical experimental data relating the genesis of inflammation of the appendix to luminal obstruction.[4, 5] In another view, minor appendicular inflammations may be regarded as commonplace near-normal states liable to aggravation, especially by luminal obstruction, to diffuse appendicitis productive of symptoms. In any event, the minor acute inflammations of the appendix reviewed in Tables I-IV were of no apparent clinical importance. It would appear illogical and somewhat dangerous to ascribe acute abdominal states to superficial inflammations of the appendix when it is appreciated that such lesions are often incidental findings (Table V).

When, indeed, is the appendix normal? If the incidence of minor inflammations, fibrosis and pinworm infestation, etc., is to be considered, the answer is just about never, but the importance of minor histologic changes can be over-rated. It would seem more important to decide, "When is a superficial appendicitis responsible for symptoms and when is it not?" This question cannot be answered by examining tissue alone. The final interpretation of the acutely but superficially inflamed appendix deserves, and indeed requires, thoughtful correlation of clinical, operative and histologic findings.[6]

SUMMARY

In this study the incidence of minor appendicular inflammations seemed to depend upon whether the pathologist observed and reported such lesions, up to a point where 35-40% of the appendices examined histologically were found to be minimally inflamed. Such inflammations were found almost as often in incidentally removed appendices as in those removed because a clinical diagnosis of acute appendicitis was made preoperatively. Therefore, minor inflammations of the appendix were not, *per se*, considered adequate to explain the symptoms leading to appendectomy, and reports of such lesions should not mislead the clinical attendant into dismissing other causes for acute abdominal pain.

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PAGES OUT OF THE PAST: FROM THE JOURNAL OF FIFTY YEARS AGO

In 1891 Robert Koch discovered the tubercle bacillus, and in 1892 demonstrated the identity of the tuberculosis of man and domestic animals. In 1901 the same great bacteriologist electrified the world by his declaration that bovine and human tuberculosis are, to all intents and purposes, distinct diseases, so rarely intercommunicable that, in the campaign against phthisis and tuberculous disease in man, the spread of bovine tuberculosis might be left wholly out of account.

The consternation that this pronouncement caused among what we may term the public health bureaucracy was profound. The danger to be apprehended from the milk and milk products of tuberculous cattle had been the prime argument employed to compel the dairy interests to accept enactments making for a purer milk supply, and now it seemed as though at one blow the valuable results of long years of work were to be destroyed. The farmer recognized that he had been put to heavy expense upon false pretences; it is no exaggeration to state that, thanks to Koch's statement, dairy legislation has been at a standstill for the last ten years.—Editorial, *Canad. M. A. J.*, 1: 978, 1911.

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JOHN O. GODDEN, M.D., C.M., M.Sc.(Med.)
Assistant to the Editor; ROBERT L. RANDALL
Editorial Offices: 150 ST. GEORGE ST., TORONTO
(Information regarding contributions and advertising will be found on the second page following the reading material.)

FLUORESCENT PROTEIN AND ANTIBODY TRACING

ONE of the more exciting avenues of research in recent years was opened with the discovery that native or foreign proteins could be labelled with certain fluorescent dyes and injected into animals or humans without appreciable effect upon their biological or immunological properties. The fluorochrome dyes commonly used in such studies at present are fluorescein and lissamine rhodamine B (RB 200). Combined with various proteins these substances form conjugates which fluoresce with an apple-green or orange appearance, respectively, in ultraviolet light, permitting their accurate tracing by ultraviolet fluorescence microscopy in suitable preparations of cells, tissues and microorganisms. Such labelled proteins are not toxic, and after injection they appear to act essentially as normal proteins, biologically and immunologically. The story of the development of this unique research tool, the minutiae of techniques involved in such studies, their current applications and future potential have recently been recounted in scholarly fashion by R. C. Nairn (*Endeavour*, 20: 78, 1961).

Fluorescent protein tracing techniques are of two types. *Direct tracing* involves the injection of conjugates of protein and fluorescent dye into animals, following which their distribution may be studied by fluorescence microscopy in various tissues *in vitro*, or sometimes by such *in vivo* techniques as microcirculatory examination of mesenteric vascular loops. The second type of fluorescent protein tracing is *immunological tracing* which is used more commonly than the direct method, from which it is quite distinct. After conjugation with one of the fluorescent dyes, serum antibody still retains a good proportion of its immunologic activity. Fuorescent antibody can thus be used to combine with and specifically stain the particular protein antigen against which it acts as an antibody. For example, if a suspension of bacteria is selected as the antigen and is injected into a rabbit two or three times over a period of a few weeks, it will stimulate the production of antibodies in the gamma globulin of the rabbit's serum. These antibodies will be specific for the protein of the injected bacteria. This antibody-containing gamma globulin can then be removed from the rabbit's serum and conjugated with one of the fluorochromes. Such a conjugate will react with its corresponding antigen in the bacteria used in the experiment, with immunologic specificity. The bacteria thus become coated with the labelled antibody and fluoresce brilliantly under ultraviolet light. Certain modifications of this technique, referred to as "sandwich" or "double layer" methods, have been developed as an alternative to the foregoing procedure. One of these "sandwich" techniques, for example, involves the coating of the antigen with unlabelled specific antibody globulin as the first step, after which the latter substance can be traced by means of a fluorescent-labelled antiglobulin serum.

These immunologic tracing procedures have now been used to study the behaviour, in experimental animals, of a wide variety of antigenic substances including various connective tissue elements, nuclear and cytoplasmic proteins, enzymes, hormones, viruses, bacteria, protozoa, fungi and other parasitic micro-organisms. The fluorescent antigen-antibody complexes in these experiments are studied in frozen tissue sections, smears, or tissue cultures.

The value of immunologic fluorescent tracing to microbiologists and immunologists became firmly established by the important studies of A. H. Coons and his co-workers on the distribution of foreign antigens, the natural history of virus infections, and the process of antibody formation.

The specific staining of bacteria by a fluorochrome-labelled antibacterial serum is one of the simplest examples of the usefulness of immunologic tracing. By this means it is possible to identify specific organisms in a mixed flora, for example Group A streptococci in throat washings. Refinements of this technique also permit the simultaneous identification of two different organisms, or even of different strains of the same organism, by double staining procedures. This double staining technique is of value, too, in the study of certain immunological problems and has been used, for example, to identify different antibody producing cells in a single lymph node.

Fluorescent antibody labelling of viruses in infected tissue culture cells and animal or human tissues is a useful tool in the study of the natural history of virus infections, their precise localization and mode of development. This method is sufficiently exact that it can clearly demonstrate whether the virus is located on the cell membrane, in the cytoplasm, the perinuclear membrane, or the nucleus. A great deal of valuable new informa-

tion has thus been acquired concerning the infectivity, growth cycles and spread of a variety of viruses.

This technique is also of value in the location of antigenic substances native to various tissues. A number of such native antigenic substances have now been demonstrated histologically by fluorescent antibody labelling, including certain enzymes (renin, pancreatic enzyme), hormones (insulin, pituitary growth hormone), plasma proteins, reticulin, basement membrane, muscle proteins and the blood group substances in gastric and duodenal mucosa.

A recent intriguing extension of this technique has demonstrated that while normal skin cells contain antigenic components specific for skin, as shown by their specific fluorescent staining with labelled anti-skin serum, the cells of malignant skin tumours do not possess this specific antigen. Other fluorescent antibody studies indicate that similar organ-specific antigens can be demonstrated in a variety of tissues and organs where they have been shown to be distributed in the surface membrane of the tissue cells. It has been suggested that such a "surface marker" might be required for recognition and control of normal cells by the body, and that the absence of this marker in cancer cells might be responsible for their uncontrolled malignant growth.

Fluorescent tracing has also contributed to the more precise and accurate demonstration of circulating antibodies of many types in the serum of man. In such cases the serum to be tested is conjugated with a fluorochrome and treated with suitable preparations of the antigen against which antibodies are suspected to exist in the serum. This procedure may aid in the diagnosis of bacterial or virus infections as a refined supplement to more time-honoured methods of demonstrating the presence of antibodies against such organisms.

It is also of particular value in detecting the presence in man of antibodies against mammalian nuclear proteins. Such non-species-specific antinuclear antibodies are now being studied with great interest and intensity in that broad group of disorders currently considered by many investigators to be "autoimmune diseases", in which antibodies developed by the subject against his own tissues are believed to be responsible for the clinical manifestations of the disease concerned. One recent investigation of note, along this line, has demonstrated that the chromosomes themselves are among the nuclear components that are affected by antinuclear antibodies in the sera of certain patients with one of the "autoimmune diseases", lupus erythematosus (Krooth, R. S. *et al.*, *Science*, 134: 284, 1961). In this study, chromosomal preparations which were first exposed to the lupus serum containing antinuclear activity, and then to horse antihuman globulin conjugated with fluorescein, exhibited marked fluorescence under ultraviolet light. This rapidly developing and fascinating field of autoimmunity has been the subject of extensive comment in recent issues of this Journal.

Fluorescent antibody tracing is thus a useful investigative tool that has already made its mark in microbiological and applied clinical research, and offers promising new avenues of approach to fundamental studies of autoimmunity and the immunological aspects of species and organ specificity, embryology, genetics and carcinogenesis.

FOLIC ACID AND PERNICIOUS ANEMIA

THE treatment of choice for pernicious anemia is vitamin B_{12}, which is readily available and easily administered parenterally. Even though it has been known for some years that folic acid can ameliorate the hematologic abnormalities of pernicious anemia, and thus obscure the diagnosis, while having no beneficial effect upon the associated crippling spinal cord degeneration of that disease, still a significant number of cases are being reported in which this combination of events has occurred as a result of treatment with folic acid, given either intentionally or inadvertently.

Two such cases are discussed by Baldwin and Dalessio.[1] One patient received 6.28 mg. of folic acid per day using a multiple vitamin preparation, and had no hematologic manifestations of pernicious anemia. The other patient, who had received 0.50 mg. of folic acid per day, also from a multiple vitamin preparation, showed macrocytosis, a low red blood cell count, and a hematocrit of 39%. In this case, the dose of folic acid was not quite sufficient to restore the blood picture to normal, although profound anemia was prevented. Both patients, however, complained of paresthesias of the limbs, and had neurological deficits in the affected extremities.

Biochemically, both vitamin B_{12} and folic acid are essential in the synthesis of nucleoproteins. It has been postulated that both act as coenzymes, but at different stages of this synthesis. Vitamin B_{12} acts earlier in the biochemical sequence, and is essential for both desoxyribose nucleic acid (DNA) and ribose nucleic acid (RNA) production, whereas folic acid is concerned only with DNA formation. DNA is found only in nuclei and chromosomes, and when the cells divide, DNA synthesis must increase if proper mitosis is to occur. Any lack of vitamin B_{12} or folic acid will disrupt this process. Tissues, such as the hematopoietic and gastrointestinal systems, in which rapid turnover and active cell division occur, will be most affected. RNA is found only in the cytoplasm and nucleolus of cells. Neural tissue, in which cell division is infrequent and DNA turnover therefore low, contains high quantities of RNA. Since folic acid has little effect on RNA synthesis, when used alone in the treatment of pernicious anemia, neural tissue integrity will fail. Vitamin B_{12} is required for RNA production. Thus, vitamin B_{12}, and *not* folic acid, is the treatment of choice for pernicious anemia.

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There has been considerable discussion over whether folic acid should be banned from use in multiple vitamin preparations to avoid masking the diagnosis of pernicious anemia.[2] In support of this proposal is the fact that mixed "shotgun" therapy is seldom warranted in medicine, and especially so when its use may result in serious, potentially irreversible nervous system damage. On the other hand, the arguments in support of retaining folic acid in across-the-counter multiple vitamin preparations are that (1) folic acid deficiency is prevalent, and withholding this vitamin from general prophylactic use may deprive the many to avoid possible jeopardy to the few, and (2) folic acid probably never completely suppresses the hematologic manifestations of pernicious anemia, and definite abnormalities are usually evident on morphologic inspection of the blood.

Recent evidence has suggested a possible solution to this problem. It has been found that more folic acid is required to initiate a hematologic response in pernicious anemia than to correct a true deficiency of folic acid itself. Thus, it may be possible to prevent folic acid deficiency by the use of readily available multiple vitamin preparations containing no more than 0.1 to 0.2 mg. of folic acid, a so-called small "physiologic dose". The total daily dose of folic acid should not exceed 0.4 mg. Larger doses should be reserved for prescribed use in patients with diseases in which large amounts of oral folic acid are specifically indicated.

Until it is more definitely known how much folic acid is "safe" when given for a long period to a patient in whom pernicious anemia is developing, it would be well for all physicians to avoid the indiscriminate use of preparations containing this agent, to use prophylactic multiple vitamin preparations containing only small amounts of folic acid when genuine nutritional support is required, and to be ever alert to the diagnosis of pernicious anemia in a patient with damage to the nervous system who has little or no associated anemia.

F.L.

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PROGRESS IN THE DETECTION OF LUNG CANCER

SUCCESSFUL programs for prevention of lung cancer on a large scale are still a distant prospect, so that any improvement in the diagnosis and treatment of this common malignancy is welcome. The promise of much earlier detection through community-wide programs of chest radiography directed to men over 45 years of age was somewhat dimmed by findings of Cuthbert of Glasgow[1] and others who showed that unselected "asymptomatic" persons in community surveys often are not truly without symptoms. In Cuthbert's study, only 12 of 48 subjects in whom lung cancer was detected in this mass miniature radiography survey had no symptoms. Eighteen months after first attending clinic, 13 of the 48 were still alive as compared with 8 of the 48 lung cancer patients with symptoms who were referred to the clinic by local practitioners. The similarity between the survival experience of the two groups is disappointing.

However, an interim report from the Philadelphia Pulmonary Neoplasm Research Project[2] demonstrates how much can be achieved by a thorough-going approach to lung cancer detection. This report concerns 6137 men and the 92 proved lung cancers found among them during follow-up periods that ranged from one-half to seven and one-half years. Of the 92 proved bronchogenic cancers, 66 were visible on entry films, a prevalence of 11 per 1000 in this particular group. Twenty-six cases of lung cancer developed during the period of observation, an incidence rate of 1 per 1000 per year. Symptoms attributable to the neoplasms often appeared before radiological abnormalities. The incidence of new, proved lung cancer was twice as high as the incidence of new, proved active tuberculosis.

The recognition that lung cancer is diagnosed relatively late in its natural course through present methods has led to great interest in the possibility of detecting malignant changes in the bronchial mucosa early by the cytological examination of respiratory tract secretions at regular intervals. The difficulty of obtaining secretions truly representative of the bronchial mucosa stimulated Barach *et al.*[3] to develop an improved technique of sputum induction for the cytological diagnosis of lung cancer and other conditions. This technique involves the use of apparatus designed to deliver a glycol-saline aerosol at a temperature between 115 and 125° F. In a preliminary study of 14 patients with suspected lung cancer, the presence of malignant cells was demonstrated by the aerosol technique in some instances when routine sputum analysis was negative.

The wider application of pulmonary cytology studies and improved techniques of inducing sputum secretions have been useful in identifying pulmonary lesions found by other means. However, the increased practice of cytological examination of sputum has created a new diagnostic quandary in which bronchial malignancy is recognized on a cytological basis at a stage when precise localization is impossible. In view of the frequency with which symptoms may precede the radiologic signs in lung cancer and in view of the evidence from Auerbach and his colleagues[4] that the epidermoid type is a multicentric lesion, this diagnostic and therapeutic dilemma may be expected to become more common.

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MEDICAL NEWS IN BRIEF

CIRCULATING ANTIBODIES IN RETICULOSES

Barr and Fairley (*Lancet*, 1: 1305, 1961) have reported on a study that was undertaken to determine responses in reticuloses in order to ascertain (a) whether patients with all forms of reticuloses respond normally on re-immunization, (b) whether patients with malignant diseases of lymphocytes respond in the same way as those with other reticuloses, and (c) whether the previous conflicting reports of antibody formation in Hodgkin's disease and myeloproliferative syndromes could be explained by a difference between the responses to primary immunization and re-immunization.

The formation of tetanus antitoxin on primary immunization with tetanus toxoid was assessed in 42 patients with reticuloses. It was found that antitoxin production was significantly impaired in all forms of reticuloses, but that patients with malignant diseases of lymphocytes (chronic lymphatic leukemia, lymphosarcoma and lymphoid follicular reticulosis) were more affected than those with other reticuloses (Hodgkin's disease, chronic and acute myeloproliferative syndromes).

The formation of antibodies on re-immunization was assessed by measuring the formation of antitoxin in 15 patients who had been immunized with tetanus toxoid in the past, and the formation of anti-A-agglutinins and hemolysins in 31 patients after immunization with tetanus toxoid. It was found that the ability to form antibodies on re-immunization was grossly impaired in patients with malignant diseases of the lymphocytes, but was normal or only slightly impaired in patients with other reticuloses.

It is suggested that possibly some of the differences between earlier reported observations on antibody formation in reticuloses may have been due to failure to distinguish between primary immunization and re-immunization.

URIC ACID EXCRETION IN GOUT: EVIDENCE OF AN ABNORMALITY IN RENAL TRANSPORT

The mechanism of hyperuricemia in gout remains in dispute. Recent evidence has suggested that uric acid transport by the kidney may be altered in gout and that this may contribute to the hyperuricemia. In a recent study by Lathem and Rodnan (*J. Clin. Invest.*, 40: 1056, 1961), the renal transport and excretion of uric acid by gouty patients were examined under conditions of acute intravenous urate loading and compared with a group of non-gouty individuals studied under similar conditions. Sodium or lithium urate was infused intravenously (16 to 32 mg. per minute) over a two-hour to three-hour period while measurements of plasma and urine urate levels were made and the glomerular filtration rate (inulin clearance) was determined. Only subjects with normal filtration rates were included. As the plasma urate level increased during the infusion, the filtered load and urinary excretion also increased. A distinct impairment in urate excretion was apparent in all of the gouty subjects studied. At comparable plasma levels (8 to 30 mg. %) and filtered loads, the gouty subjects excreted a consistently and significantly smaller proportion of the filtered urate load (from one-half to four-fifths less) than the non-gouty controls. This was also true of one of two subjects with essential hyperuricemia studied. In two-thirds of the control subjects the difference between the filtered load and the excretory rate (minimum reabsorptive rate) became constant (average, 10 mg. per minute) at high plasma levels. In all of the gouty subjects the minimum reabsorptive rate increased progressively and did not become constant, attaining values of 20 or more mg. per minute. These results established that an abnormality in renal urate transport —either increased reabsorption or decreased secretion— exists in gout. This abnormality may be a basic feature of the metabolic disorder of gout or may be acquired or appear as an adaptative response during the course of the disease.

GENES AND ANTIBODIES

Nine theories of antibody formation are presented and discussed by Lederberg in an issue of the *Stanford Medical Bulletin* (19: 53, 1961):

1. *Antibody Gobulin.* The stereospecific segment of each antibody globulin is determined by a unique sequence of amino acids.
2. *Gene for Globulin Synthesis.* The cell making a given antibody has a correspondingly unique sequence of nucleotides in a segment of its chromosomal DNA: its "gene for globulin synthesis".
3. *Genic Diversity of Precursor Cells.* The genic diversity of the precursors of antibody-forming cells arises from a high rate of spontaneous mutation during their lifelong proliferation.
4. *Hypermutability.* This hypermutability consists of the random assembly of the DNA of the "globulin gene" during certain stages of cellular proliferation.
5. *Spontaneous Production of Antibody.* Each cell, as it begins to mature, spontaneously produces small amounts of the antibody corresponding to its own genotype.
6. *Induction of Immune Tolerance.* The immature antibody-forming cell is hypersensitive to an antigen-antibody combination: it will be suppressed if it encounters the homologous antigen at this time.
7. *Excitation of Massive Antibody Formation.* The mature antibody-forming cell is reactive to an antigen-antibody combination: it will be stimulated if it first encounters the homologous antigen at this time. The stimulation comprises the acceleration of protein synthesis and the cytological maturation which mark "plasma cells".
8. *Proliferation of Mature Cells.* Mature cells proliferate extensively under antigenic stimulation but are genetically stable and therefore generate large clones genotypically pre-adapted to produce the homologous antibody.
9. *Persistence of Clones.* These clones tend to persist after the disappearance of the antigen, retaining their capacity to react promptly to its later reintroduction.

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ASSOCIATION NEWS

FUTURE REQUIREMENTS FOR PHYSICIANS IN CANADA

A report prepared by Mr. Guy C. Clarkson, M.A., of the Department of Medical Economics, The Canadian Medical Association, as an exhibit for presentation to The Royal Commission on Health Services.

In the preliminary submission from The Canadian Medical Association to the Royal Commission on Health Services it was stated:

> "A rough measure of adequacy of medical services is the physician-population ratio. During the period 1900-1950 the national ratio in Canada has been, with remarkable constancy, of the order of 1:980. We estimate that the current ratio is 1:888,* a more favourable figure than we have ever enjoyed, and one which compares favourably with that of the more advanced countries of the Western world. It will be appreciated that ratios of the type mentioned here represent gross figures of medically qualified persons and that not all of the doctors are engaged in the care of patients. We are conscious, moreover, that medical immigration during the past 10 years has contributed materially to Canada's medical manpower and that without this advantage, which may be temporary, the physician-population ratio would have deteriorated. In other words, we are not producing enough doctors in Canada to keep pace with our rapidly expanding population. The supply is just adequate under current conditions of practice and almost certainly would be inadequate to staff new and demanding areas of health services."

In this present document we have collated existing information in as specific a form as is possible. Unfortunately, much of the data are not precise, as they evolve from informed estimates and somewhat inexact statistics. We have used this information, with these acknowledged limitations, to examine current trends, to project requirements for medical doctors in Canada, to examine our sources of supply and to assess the ability of our Canadian medical schools to produce the number of medical graduates which will be required in the future.

PART I.

THE NUMBER OF PHYSICIANS IN CANADA

The Physician-Population Ratio

One method of assessing the requirements for physicians is to examine the physician-population ratio. Table I shows the historical record of the number of doctors in Canada, from the beginning of this century until 1951, and the ratio which this number bears to the total population of the country.

While Table I shows that the national physician-population ratio has not changed appreciably during the first half of the century, Table II, which deals with this subject in detail for the last 10 years, shows that the national physician-population ratio has improved by over 100 persons per physician in this relatively short period. An analysis of these figures on a provincial basis is presented in Appendix A.

This improvement from 989 persons per physician in 1951 to 879 persons per physician in 1960 is a change of more than 10% in the relative supply of doctors and a rate of improvement of more than 1% per annum. The assimilation of this relatively more plentiful supply indicates a readiness on the part of the public to use the services of a greater number of doctors. We have, however, experienced a substantial inflow of immigrant physicians during this period and this improvement has resulted to a great extent, if not entirely, from this source of supply.

TABLE I.—PHYSICIAN-POPULATION RATIOS IN CANADA TEN-YEAR PERIODS, 1901 TO 1951

Year	*Estimated No. of doctors*	*Population*	*Physician-population ratio*
1901.....	5475	5,371,000	1: 981
1911.....	7411	7,207,000	1: 972
1921.....	8706	8,788,000	1:1009
1931.....	10,020	10,377,000	1:1036
1941.....	11,873*	11,507,000	1: 969
1951.....	14,163	14,009,000	1: 989

Source: Department of National Health and Welfare Survey of Physicians—1954.

*The 1941 figure includes 1150 armed forces' doctors because of wartime conditions. The other figures exclude doctors in the armed forces since these data were not available up to 1931 and the number of doctors serving in Canada in peacetime is nominal.

TABLE II.—ESTIMATED PHYSICIAN-POPULATION RATIOS CANADA, 1951 TO 1960

Year	*Estimated No. of doctors* (Dec. 31)*	*Estimated population corresponding year and month†*	*Physician-population ratio*
1951 (June)...	14,163	14,009,000	1:989
1952.....	15,135	14,649,000	1:968
1953.....	15,829	15,195,000	1:960
1954.....	16,431	15,698,000	1:955
1955.....	17,221	16,081,000	1:934
1956.....	17,871	16,589,000	1:928
1957.....	18,523	17,048,000	1:920
1958..... ...	19,096	17,284,000	1:905
1959.....	19,800	17,678,000	1:893
1960.....	20,517	18,041,000	1:879

Sources: *Canadian Medical Association questionnaire to Registrars of Provincial Licensing Authorities, except for 1951 which is based on census data.
†Dominion Bureau of Statistics.

Whether or not this improvement in the physician-population ratio need continue unabated is open to question. Some further improvement would seem necessary if during the next 20 years we experience the expected increase in proportion of persons in the older age groups. These persons require a greater number of services than do those in the younger age groups. We have also found that insured persons seek more services than non-insured persons. The logical and expected expansion of the proportion of the population covered by private insurance suggests to us an increased demand for the services of doctors.

*Ratio for September 1, 1960.

We have, therefore, prepared two sets of statistics for future requirements—one assuming that the supply of doctors and the demand for services will remain constant at the December 1960 level of 1:879, and the other assuming a continual improvement in this ratio, although at the more conservative rate of one-half of one per cent (0.5%) per annum. This latter assumption produces the following physician-population ratios at one-year intervals up to 1980.

Year	*Ratio*	*Year*	*Ratio*	*Year*	*Ratio*
1960	1:879	1967	1:849	1974	1:819
1961	1:875	1968	1:845	1975	1:815
1962	1:870	1969	1:840	1976	1:811
1963	1:866	1970	1:836	1977	1:807
1964	1:862	1971	1:832	1978	1:803
1965	1:857	1972	1:828	1979	1:799
1966	1:853	1973	1:824	1980	1:795

From the improving ratios quoted above and the constant ratio of 1:879, it is possible to produce two projections of total doctor requirements up to 1980, based on the population projections calculated by the Royal Commission on Canada's Economic Prospects. No comment on distribution is implied in these projections of doctor requirements although we know that some unevenness exists in the physician-population ratio in regional and rural-urban settings.

Population Projections

The Royal Commission on Canada's Economic Prospects estimated four possible levels of population in Canada for 1960, 1965, 1970, 1975 and 1980. These projections depended, among other things, on the level of net immigration. The Commission's highest population projections were based on a net immigration rate of 100,000 per annum. Other rates assumed were 75,000 50,000 and zero.

TABLE III.—POPULATION PROJECTION—ROYAL COMMISSION ON CANADA'S ECONOMIC PROSPECTS

	Projected population for net immigration level of	
Year	*75,000*	*100,000*
1965	19,520,000	19,820,000
1970	21,640,000	22,130,000
1975	23,990,000	24,660,000
1980	26,650,000	27,530,000

Source: Report of the Royal Commission on Canada's Economic Prospects.

The official population in 1960 exceeded the Commission's highest projection by 164,000 persons, being 17,814,000 in June instead of 17,650,000. If this trend continues, the Commission's highest projections up to 1980 may well prove to be a legitimate basis for the projection of doctor requirements. If, however, there is a continuation of the current downward trend in net immigration, the Commission's projections based on a net immigration of 75,000 per annum may be applicable. We consider it reasonable, therefore, to use the Commission's population projections based on net immigration levels of 75,000 and 100,000, for the purpose of showing doctor requirements. These two levels of population projection are shown in Table III.

Projected Doctor Requirements Based on the Two Projected Levels of Population and Constant and Improving Physician-Population Ratios

By dividing the population shown above (and the intervening interpolations) by the physician-population ratios previously determined, we are able to calculate the approximate total annual requirements for doctors up to 1980. These are shown in Table IV at selected two-year and three-year intervals.

TABLE IV.—PROJECTED DOCTOR REQUIREMENTS

	Constant ratio 1:879		*Improving ratios 1:879 to 1:795*	
Year	*No. of doctors for minimum population*	*No. of doctors for maximum population*	*No. of doctors for minimum population*	*No. of doctors for maximum population*
1962	21,040	21,180	21,260	21,390
1965	22,210	22,550	22,770	23,120
1967	23,110	23,660	23,940	24,400
1970	24,620	25,180	25,880	26,470
1972	25,660	26,300	27,250	27,930
1975	27,290	28,060	29,420	30,250
1977	28,460	29,310	30,990	31,920
1980	30,320	31,320	33,520	34,620

This table indicates various projected increases in requirements for medical manpower in Canada, ranging by 1980, from a minimum increase of about 48% to a maximum increase of about 69% over 1960 levels. These figures, both past and future, are gross numbers, including registered doctors who are engaged in fields other than the treatment of patients. They include doctors working in administrative capacities, those doing research, those in industry and those in post-graduate training, as well as those over the age of 65. In our projections for the next two decades we have assumed that similar allowances must be made for doctors working in similar capacities. In so doing, we anticipate that the proportion of physicians so engaged will not change appreciably during the period.

PART II.

THE MEANS FOR SUPPLYING CANADIAN PHYSICIAN REQUIREMENTS

The foregoing section has concerned itself with establishing the existing ratio of physicians to population and the projected future requirements for doctors. This section will concern itself with a consideration of the supply of doctors needed to meet these future requirements.

There are two sources of supply of Canadian doctors, the Canadian medical schools and foreign graduates who emigrate to Canada. The record of output of Canadian medical schools is known—although even the total supply from this source is obscured by the number of Canadian graduates who leave the country to practise elsewhere or who return at an undetermined date after prolonged absence. The record of supply from foreign sources began only in 1953, when the Department of Citizenship and Immigration started to separate the occupations of all immigrants in the different professions. The numbers of immigrant physicians which we have received since that date are shown in Table V.

Table V shows that during the period 1953 to 1960 Canada received 3370 immigrant doctors. In the same period Canadian medical schools gradu-

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TABLE V.—PHYSICIAN AND SURGEON IMMIGRANTS INTO CANADA, 1953 TO 1960

National origin	*1953*	*1954*	*1955*	*1956*	*1957*	*1958*	*1959*	*1960*	*Total*
Austrian	13	6	7	8	5	4	—	2	45
British	195	160	195	214	311	202	182	162	1621
Chinese	33	1	15	5	—	5	29	20	78
East Indian	1	1	—	3	11	10	19	25	70
French	9	1	1	6	8	5	5	1	36
German	40	23	20	31	18	15	9	11	167
Hungarian	6	2	1	31	117	9	2	8	176
Italian	6	1	3	14	10	12	15	13	74
Jewish	16	13	9	11	49	18	23	9	148
Netherlander	20	27	11	6	11	16	16	10	117
Polish	14	18	7	5	6	8	9	4	71
Spanish	3	2	2	8	9	10	22	32	88
U.S.A.	55	39	33	29	46	52	66	84	404
Others	21	17	29	44	34	28	42	60	275
Totals	402	311	333	415	635	394	439	441	3370

Source: Department of Citizenship and Immigration.

ated 6874 new doctors. It is difficult to say how long, on the average, it takes for these two varied groups of doctors to obtain full registration. Some British doctors obtain immediate registration in certain provinces, while some other immigrants may take several years. Some Canadian graduates also may extend their intern training for more than one year. If we say, however, that between these two extremes, we are going to assume an average period of delay of one year before each potential doctor enters the fully registered lists, we are probably coming fairly close to a reasonable approximation. On this basis, we find that domestic and immigrant sources could have contributed 8940 new registered doctors to the Canadian scene between 1953 and 1960. In actual fact, however, the supply of Canadian doctors rose by only 5382 during this period. A comparison of these two figures, an increase of only 5382 actual doctors out of a potential total of 8940, highlights a major problem in projecting the number of new doctors that must be injected into the stream each year in order to reach a given level of supply. Obviously, there must be a considerable degree of loss or attrition in the medical force each year. This attrition arises both from the older doctors who die or retire, and from the new graduates who may go to some other country either to continue their studies or to engage in practice. Some immigrants may also pass on to other countries after staying in Canada for only a limited time. The degree of loss from each of these causes cannot be isolated, but must be treated as part of a composite loss from all sources. The discovery and application of the rate of this loss are of critical importance in being able to project the future rates at which Canadian medical schools must graduate new doctors and/or the rate at which we must receive new immigrant doctors.

The calculation of this rate of attrition for the past seven years, the only period for which the input of both new immigrant doctors and new Canadian graduates is known, is shown in Table VI. Starting at December 31, 1953 (equivalent to January 1, 1954), with an actual supply of 15,829 doctors, we have added the number of Canadian graduates in 1953 and the number of immigrant physicians who entered the country during 1953 (both of which groups would then have had the opportunity to qualify for full registration), which gives a theoretical total of 17,056 doctors at the end of 1954. In actual fact, however, there were only 16,431 doctors registered on December 31, 1954, so that there was a loss or attrition of 625 doctors out of an average number for the year of 16,130. This is equivalent to a rate of attrition of 3.87%. Repeating this process for the period as a whole up to December 31, 1960, we are able to determine an average attrition for the seven years. This calculation is shown in Table VI.

This table indicates that the rate of attrition since 1954 has averaged 3.35%. Although it would be desirable to determine the rate of attrition from the actual experience of the individual members of the medical profession during these years, these data are not available. We do know, however, that the 3.35% rate will have been influenced by such factors as the Hungarian uprising of 1956-57, which caused an abnormally high influx of Hungarian doctors into Canada whose experience while here probably includes an abnormally high rate of attrition. This is one of the factors that might indicate that the 3.35% rate may be somewhat high, especially when we note the downward trend below 3% in the last two years.

Looking to the future, however, the development of pension plans specifically designed for doctors may

TABLE VI.—AVERAGE ATTRITION AMONGST CANADIAN DOCTORS FOR THE PERIOD 1954 TO 1960

Year	*Number of doctors at start of year*	*Additions during year*		*Theoretical total*	*Actual total at end of year*	*Loss in numbers*	*Average No. of doctors in year*	*Per cent attrition*
		Canadian graduates	*Immigrant doctors*					
1954	15,829	825	402	17,056	16,431	625	16,130	3.87
1955	16,431	896	311	17,638	17,221	417	16,826	2.48
1956	17,221	894	333	18,448	17,871	577	17,546	3.29
1957	17,871	816	415	19,102	18,523	579	18,197	3.18
1958	18,523	893	635	20,051	19,096	955	18,809	5.08
1959	19,096	828	394	20,318	19,800	518	19,448	2.66
1960	19,800	859	439	21,098	20,517	581	20,158	2.88
Average attrition								3.35

TABLE VII.—PROJECTED ANNUAL REQUIREMENTS FOR ADDITIONAL DOCTORS FROM BOTH DOMESTIC AND IMMIGRANT SOURCES 1965, 1970, 1975 AND 1980

Year	Population	Ratio	Total doctor requirements	Additional doctors required for			Additional doctors from domestic and immigrant sources
				Population increase	Improving ratio ·	Attrition at 3%	
	1. Lower population projection—constant physician-population ratio						
(June)							
1965	19,520,000	1:879	22,210	390	—	660	1050
1970	21,640,000	1:879	24,620	510	—	740	1250
1975	23,990,000	1:879	27,290	560	—	820	1380
1980	26,650,000	1:879	30,320	640	—	910	1550
	2. Lower population projection—improving physician-population ratio						
(June)							
1965	19,520,000	1:857	22,770	390	120*	680	1190
1970	21,640,000	1:836	25,880	510	150*	780	1440
1975	23,990,000	1:815	29,420	560	190*	880	1630
1980	26,650,000	1:795	33,520	640	230*	1000	1870
	3. Higher population projection—constant physician-population ratio						
(June)							
1965	19,820,000	1:879	22,550	460	—	670	1130
1970	22,130,000	1:879	25,180	550	—	760	1310
1975	24,660,000	1:879	28,060	600	—	840	1440
1980	27,530,000	1:879	31,320	690	—	940	1630
	4. Higher population projection—improving physician-population ratio						
(June)							
1965	19,820,000	1:857	23,120	460	130*	690	1280
1970	22,130,000	1:836	26,470	550	160*	800	1510
1975	24,660,000	1:815	30,250	600	190*	910	1700
1980	27,530,000	1:795	34,620	690	240*	1040	1970

*The figures shown in Table VII are for 1965 over 1964; 1970 over 1969; 1975 over 1974 and 1980 over 1979, taking into account the gradual improvement in the ratios shown on page 1163 (the physician-population ratios at one-year intervals up to 1980, assuming a continual improvement in the ratio of 1:879 at the rate of 0.5% per annum).

create an increasing trend toward earlier retirement, with consequently greater attrition from this factor. It may not be wise, therefore, to estimate a future average rate of attrition below 3%, or as high as 3.35%, as indicated above. For these reasons, we have decided to assume a flat rate exactly at the 3% level for future calculations of attrition.

The Projected Annual Input of Doctors From Canadian and Immigrant Sources, Required to Provide the Projected Levels of Medical Manpower in Canada, up to 1980

On the basis of this assumption, it is now possible to project the total number of new doctors that it will be necessary to inject into the mainstream of the Canadian physician supply each year, to make that stream grow to the projected size required. It is necessary to emphasize that the annual requirements which will be indicated are those which will be required from a combination of domestic and immigration sources, and not from Canadian medical schools alone.

In order to produce the number of new doctors which must be introduced into the mainstream of doctor supply each year, it is necessary to consider three factors:

1. Those new doctors who will be required annually purely to keep pace with the projected increases in population—at a ratio of one doctor for each 879 persons.
2. Those additional new doctors who will be required annually in order to improve the physician-population ratio by 0.5% annually, reaching a level of 1:795 in 1980.
3. Those new doctors required annually to replace other doctors lost through the various causes of attrition, at the rate of 3% of the total each year.

It will be realized that these three factors must be considered in the light of both our higher population projection and the lower one. Again, we may choose to consider only the number of doctors which must be added to the stream at the constant 1:879 physician-population ratio or at the improving (up to 1:795) ratio. Both these latter points will affect the number of doctors needed as replacements—since the greater the total number of doctors required, the greater will be the attrition at the rate of 3% of the total. In order to illustrate how these considerations may be applied in practice, we have outlined a table for each of the four main sets of circumstances which need to be considered, i.e. for the higher population projection—the upper (improving ratio) and lower (constant ratio) calculations of annual new doctor requirements; and for the lower population projection, a similar set of two calculations. These are shown in Table VII.

This table illustrates how the total annual requirements for new doctors are built up. It gives four prospective levels of new doctor requirements based on varying considerations. We must now consider these requirements in the light of the present capacity of our medical schools to graduate new doctors. In order to simplify this presentation however, and to provide definite objectives to work toward, we have decided to take the median point between our highest and lowest projected requirements and to discuss only these requirements in terms of our present medical school capacity. The median requirements, year by year up to 1974-75 and 1979-80, are as follows:

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Year	Median doctor requirements
1960 - 61	1100
1961 - 62	1115
1962 - 63	1130
1963 - 64	1145
1964 - 65	1165
1965 - 66	1230
1966 - 67	1265
1967 - 68	1300
1968 - 69	1335
1969 - 70	1370
1970 - 71	1400
1971 - 72	1435
1972 - 73	1470
1973 - 74	1505
1974 - 75	1540
1979 - 80	1760

These median requirements will provide a slightly improving physician-population ratio for both the lower and upper population projections. They reflect a population trend that is lower on the average in the period from 1961 to 1965 than was the case from 1956 to 1961, followed by a major upward change in direction in 1965-66 which continues to the end of the projected period. Since these requirements are somewhat in excess of current levels of medical school output, however, it will be necessary to consider to what extent we will have to rely upon immigration to fulfil our requirements. During the next four years the number of immigrants we will need will be governed by the number of students that are already in the training stream. This group of students has already predetermined the approximate number of graduates which will be produced, since, on a national average for the five most recent graduating classes we have received 85 graduates for every hundred first-year medical students. On this basis we are able to project the estimated total number of graduates up to 1963-64, and by deducting these from our median requirements, to arrive at the number of immigrants we will probably require to fill our annual quota of new doctors. This is shown in Table VIII.

TABLE VIII.—THE PROJECTED REQUIREMENTS FOR IMMIGRANT PHYSICIANS UP TO 1963-64, ON THE BASIS OF PROJECTED TOTAL REQUIREMENTS LESS THE ESTIMATED ACTUAL NUMBER OF MEDICAL SCHOOL GRADUATES

Year	Total doctor requirements	Estimated No. of graduates	Residual No. of immigrants required
1960 - 61	1100	825	275
1961 - 62	1115	840	275
1962 - 63	1130	805	325
1963 - 64	1145	820	325

This table shows that the level of physician immigration required in the period up to 1963-64 will reach 325 in the latter two years. During the past 10 years, the immigrant inflow as shown in Table V averaged about 420 doctors per annum. In looking to the future, however, it is necessary to take a cautious view of the number of immigrants which we will receive. It may well be that the conditions which fostered past levels of physician immigration will not apply to the same degree. However, we do not consider it unreasonable to assume that we may continue to receive an average number approximating the number we will need to receive in 1963-64, namely 325 per year. By deducting this number of immigrants from our projections of total annual new doctor requirements, we are able to estimate the approximate number of new graduates that it will be necessary for our medical schools to produce up to 1969-70 and for the years beyond. We have adopted this method rather than assuming that doctor immigration will form a certain proportion of total immigration, since medical immigration, on the whole, will not be influenced by the same factors that affect the larger mass of immigrants. Our calculations on the basis of an annual inflow of 325 doctors, therefore, are shown in Table IX.

TABLE IX.—PROJECTED REQUIREMENTS FOR MEDICAL SCHOOL GRADUATES UP TO 1974-75 AND 1979-80, ON THE BASIS OF TOTAL REQUIREMENTS LESS THE PROJECTED NUMBER OF IMMIGRANTS

Year	Total doctor requirements	Projected immigration	Canadian medical school graduates required
1964 - 65	1165	325	840
1965 - 66	1230	325	905
1966 - 67	1265	325	940
1967 - 68	1300	325	975
1968 - 69	1335	325	1010
1969 - 70	1370	325	1045
1970 - 71	1400	325	1075
1971 - 72	1435	325	1110
1972 - 73	1470	325	1145
1973 - 74	1505	325	1180
1974 - 75	1540	325	1215
1979 - 80	1760	325	1435

The peak number of graduates produced by Canadian medical schools was 896 in 1953-54. This table indicates that they will have to be able to produce a number of graduates in excess of the 900 mark by 1965-66. Whether the facilities and staff are presently equal to this task is a matter for urgent consideration, since in order to produce 905 graduates in 1965-66, an estimated first-year class of about 1065 students will have to begin their studies in the fall of 1962—only one year from now. This introduces the question of the required future enrolment capacity of Canadian medical schools, given the stated levels of graduation.

Enrolment Implications For Canadian Medical Colleges

The foregoing Table IX shows the apparent need for medical graduates up to 1974-75 and 1979-80. Translated into terms of first-year enrolment, in the professional medical colleges, these requirements would be as follows:

TABLE X.—REQUIRED FIRST-YEAR ENROLMENT IN CANADIAN MEDICAL COLLEGES

Year	First Year Enrolment
1962-63	1065
1963-64	1105
1964-65	1145
1965-66	1185
1966-67	1225
1967-68	1265
1968-69	1305
1970-71	1345
1971-72	1430
1976-77	1690

TABLE XI.—MEDICAL ENROLMENT IN CANADA BY YEAR OF COURSE
1948-49 to 1960-61

Year	Year of Course				Total Enrolment	Graduates
	First	Second	Third	Fourth		
1948-49	887	765	842	739	3233	679
1949-50	897	798	761	822	3278	791
1950-51	960	880	844	805	3489	858
1951-52	873	891	858	836	3458	783
1952-53	918	809	865	852	3444	825
1953-54	982	901	844	916	3643	896
1954-55	968	903	881	837	3589	894
1955-56	1035	883	877	856	3651	816
1956-57	1001	934	855	865	3655	893*
1957-58	1012	916	928	830	3686	828
1958-59	986	911	867	904	3668	859
1959-60	946	882	863	858	3549	863
1960-61	970	842	853	843	3508	845
TOTALS	12,435	11,315	11,138	10,963	45,851	10,830
Each year as % of Total	27.12	24.68	24.29	23.91	100.00	

*It is apparent that about 30 of these graduates are holdovers from the previous year.
Source: Association of Canadian Medical Colleges.

As mentioned before, this table shows that Canadian medical school first-year enrolment will have to increase in the fall of 1962 to a level of 1065 students from an estimated 1961-62 first-year enrolment of 1010, an increase of 55 students. The 1962-63 first-year student quota, if it is filled, would be somewhat in excess of the peak number of first-year students which has been handled in the past. By 1966-67, the additional student places needed for first-year entrants alone could be approximately 200 in excess of the previous maximum, and by 1970-71 the excess could reach 400. The only factor which could mitigate these projections somewhat is the enrolment of a student body with a lower drop-out rate than has been experienced during recent years.

The Effect on Total Enrolment

An increase in enrolment and the provision of facilities for first-year students automatically requires that facilities for second-year, third-year and fourth-year students also be enlarged. Table XI shows the relationship of enrolment in all four years of the course, to the total enrolment, for the years from 1948-49 to 1960-61.

This table illustrates that, on the basis of past experience, for every first-year student, 2.7 other student places must be provided for the combined enrolment in the three subsequent years. When a rapid rise in first-year enrolment is projected, however, total enrolment will not immediately increase on a proportionate basis, owing to the previously smaller first-year classes who are now in their second, third and fourth years. For this reason, total enrolment for any period of rapid expansion must be projected on a course-year by course-year basis, taking into account the drop-out from one course-year to another. On the basis of this "drop-out" experience for the five most recent graduating classes, these projections would be as shown in Table XII.

This table must be considered only as an approximation and as a broad guide to the future. It is designed to give some idea of overall enrolment capacity requirements during the next decade. It will be noted in this respect that the projected total enrolment in 1962-63 of 3630 would still be less than the maximum of 3686 that has been accommodated in the past. Table XI shows that this level was reached in 1957-58. By 1963-64, however, Canadian medical schools may

TABLE XII.—ESTIMATED TOTAL NUMBER OF STUDENT PLACES REQUIRED IN CANADIAN MEDICAL SCHOOLS, 1962-63 to 1971-72 AND 1976-77

Academic year	Year of Course				Total enrolment	Projected graduates
	First year	Second year	Third year	Fourth year		
1960-61*	970	842	853	843	3508	845
1961-62	1010†	883	811	836‡	3540	840
1962-63	1065	919	850	796‡	3630	805
1963-64	1106	969	890	836	3800	820
1964-65	1145	1006	940	869	3960	840
1965-66	1185	1042	975	918	4120	905
1966-67	1225	1078	1006	951	4260	940
1967-68	1265	1115	1045	985	4410	975
1968-69	1305	1150	1075	1020	4550	1010
1969-70	1345	1188	1112	1055	4700	1045
1970-71	1385	1224	1143	1088	4840	1075
1971-72	1430	1260	1187	1123	5000	1110
1976-77	1690	—	—	—	5900	1300

*Actual. †Preliminary estimate—Association of Canadian Medical Colleges.
‡These fourth-year figures fall slightly short of the number of graduates projected on the basis of 85% of first-year enrolment. This is because the drop-out rate for these classes in their first two or three years has been slightly greater than for the five classes for which the 85% graduation rate was calculated. This is probably a temporary phenomenon which will be corrected.

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find their accommodation and teaching facilities somewhat overextended unless some improvements can be made quickly. It is known that several expansions are now under way or are being planned. The long period of time which is required to put new facilities into operation, however, indicates that urgent action may be needed to meet the projected total requirements in 1971-72 which may exceed present capacity by 35%. It might also be noted in passing, in this discussion, that for every first-year professional medical faculty student, the universities, as distinct from the medical schools, will have to provide at least two places (one for each year) for pre-medical students.

CONCLUSION

With all due allowance for an element of inaccuracy in the data here presented, the conclusion is inescapable that the output and capacity of Canadian medical schools requires to be increased substantially in the almost immediate future. If this is accepted and regarded as a legitimate objective, we must attract to a career in medicine a higher proportion of academically qualified candidates than are now presenting themselves, and the facilities and personnel to train them must be made ready. It is possible that the entry and output of certain existing Canadian schools can be increased, and this appears to offer the most likely prospect for early augmentation of the native medical force. In the case of certain of the larger medical schools the optimum size of class appears to have been reached and the possibility of further expansion is remote.

There remains the possibility of establishing new medical schools at Canadian universities where faculties of medicine are not now functioning. Long-range planning is essential to the implementation of such a proposal, and a declaration of need by the Royal Commission on Health Services might encourage certain interested universities to commence the assembling of money, buildings and, above all, teachers, in the pre-medical, pre-clinical and clinical phases of medical training. The time lag between the decision to establish a new medical school and the emergence of the first graduate may well be represented by an interval of 12 years. In view of the predictions made in this document on the future needs of this country for doctors, a beginning must shortly be made on several new medical schools.

The improvement and expansion of Canada's health services will in large measure depend upon the availability of well-qualified physicians. This analysis of the situation in medical manpower as we foresee it is intended to ensure that services of the highest quality will not be impaired by the lack of the essential medical personnel to operate them.

APPENDIX A

Provincial Aspects of Physician Registration and Supply

The following tables (A1 to A4) are an elaboration on a provincial basis of the national physician-population ratios noted in Table II in the main body of this report. They are derived from the replies to a questionnaire sent to all provincial medical licensing authorities in January 1961. The tabulation is divided into three parts: for the years 1950 to 1960, as follows:

TABLE A1 — The total number of doctors registered as of December 31 of each year.

TABLE A2 — New registrants who were graduates of Canadian schools.

TABLE A3 — New registrants who were graduates of foreign schools.

The requirements for registration vary slightly from province to province, but it may be stated in general terms that candidates for a license to practise medicine must have:

(a) Graduated from a recognized medical school.

(b) Satisfactorily completed one year as an intern in a hospital.

(c) Passed the examinations of the Medical Council of Canada or its provincial equivalent.

(d) Complied with the ethical, educational and fee requirements of the licensing authority.

The major exception to this statement of requirements is that persons registered in the "home list" of the General Medical Council of Great Britain may register without further examination in Alberta, Saskatchewan, Manitoba, Nova Scotia, Prince Edward Island and Newfoundland. This circumstance has resulted in a large intake of immigrant physicians from the United Kingdom in the reciprocating provinces.

It is significant that in several of the provinces, particularly those which reciprocate with the G.M.C., registration of non-Canadians has exceeded that of Canadian graduates in several of the years under study. The cumulative effect has been to change the medical population of these provinces from one predominantly Canadian to one in which the medical skills of many nations are very adequately represented.

It will be noted in Table A2 that the numbers of new registrants who are graduates of Canadian schools have a tendency to exceed the actual output of graduates from these schools. It is not uncommon for a Canadian doctor to register and maintain his licence to practise in more than one province, thereby accounting for this anomaly.

Likewise, the figures reported by the Registrars for registration of graduates of foreign schools are higher than those of physician immigration provided by the Department of Citizenship and Immigration in Table V of the main report. This apparent discrepancy reflects the extreme mobility of our immigrant physicians. The statistics for Newfoundland, in particular, and other provinces to a lesser degree indicate that many of these physicians stay a relatively short time in their first province for registration and then move on to another province.

The table of total registrations (Table A1) as reported by the Registrars, however, records only those doctors who are resident and practising in each province and thus should eliminate those who only register temporarily or who maintain a multiple registration but only practise in one province. That many registrations are very transient may be noted by comparing the total number of new registrations—both domestic and foreign—in most provinces in a given year, with the actual increase in the number of doctors in that province in that year, as given in Table A1. The

TABULATION OF RESULTS RECEIVED FROM QUESTIONNAIRE SENT TO PROVINCIAL MEDICAL LICENSING AUTHORITIES

TABLE A1.—TOTAL FULLY REGISTERED, ACTIVE, RESIDENT PHYSICIANS
(DECEMBER 31 OF EACH YEAR)

Province	1950	1951	1952	1953	1954	1955	1956	1957	1958	1959	1960	Physician/ population ratio Dec. 31, 1960
Nfld.	154	163	178	200	199	215	228	251	241	275	277	1:1682
P.E.I.	NA	NA	69	81	83	80	83	82	81	80	87	1:1207
N.S.	NA	582	609	NA	642	670	678	703	712	693	719	1:1013
N.B.	337	337	353	360	373	385	378	400	410	431	445	1:1362
Quebec	4145	4150	4311	4452	4559	4793	4905	5163	5397	5622	5863	1: 883
Ontario	5523	5642	5822	6119	6400	6704	7064	7240	7409	7600	7908	1: 780
Manitoba	775	780	799	833	866	906	912	947	969	1003	1033	1: 879
Sask.	633	662	713	750	776	811	835	864	886	925	895	1:1019
Alberta	780	804	863	916	963	995	1041	1097	1141	1221	1280	1:1023
B.C.	NA	NA	NA	1493	1570	1662	1747	1776	1850	1942	2010	1: 810
TOTALS	—	—	—	—	16,431	17,221	17,871	18,523	19,096	19,800	20,517	1: 879

TABLE A2.—NEW REGISTRANTS—GRADUATES OF CANADIAN SCHOOLS

												Total
Nfld.	23	14	18	15	30	14	29	22	37	27	24	253
P.E.I.	2	3	3	9	1	7	1	3	5	5	5	44
N.S.	30*	31	53	50*	49	39	48	55	40	46	43	484
N.B.	14	30	25	5	21	11	13	14	18	7	23	181
Quebec	235	277	229	235	288	286	235	269	298	274	323	2949
Ontario	297	305	297	335	304	344	343	307	221	224	266	3243
Manitoba	59	45	47	48	51	55	45	42	34	38	37	501
Sask.	45	62	63	50	42	47	44	48	40	35	30	506
Alberta	57	49	73	61	47	45	60	48	45	62	72	619
B.C.	86	86	109	91	100	106	91	83	81	93	99	1025
TOTALS	848*	902	917	899*	933	954	909	891	819	811	922	9805

TABLE A3.—NEW REGISTRANTS—GRADUATES OF FOREIGN SCHOOLS

												Total
Nfld.	15	29	50	61	94	49	77	53	74	74	83	659
P.E.I.	2	2	1	1	0	0	0	1	2	3	1	13
N.S.	16*	16	18	17*	17	23	34	40	32	42	64	319
N.B.	3	3	1	1	4	5	5	1	3	4	7	37
Quebec	1	0	0	5	13	17	19	51	45	38	36	224
Ontario	52	64	84	125	160	158	179	198	203	192	135	1550
Manitoba	25	27	37	38	48	42	49	54	49	66	50	485
Sask.	33	44	43	43	41	48	49	69	54	62	50	536
Alberta	34	52	61	59	59	57	50	72	51	57	51	603
B.C.	15	24	44	43	52	48	34	43	44	48	45	440
TOTALS	196*	261	339	393*	488	447	496	582	557	586	521	4866

NA—not available. *Estimated.

stability of the total registration figures in the face of these somewhat erratic influences gives further support to their validity.

Table A4 portrays the estimated physician-population ratios in each province at two-year intervals from 1950. These are based on the estimated provincial populations as at December 31 of each year. This table shows the relative trends in each province. While the physician-population ratios vary greatly from province to province, there is not a single province in which considerable improvement has not taken place over the past 11 years.

TABLE A4.—ESTIMATED PHYSICIAN—POPULATION RATIOS BY PROVINCES
DECEMBER 31, 1950, 1952, 1954, 1956, 1958 AND 1960

	1950		1952		1954		1956		1958		1960	
Province	Number of physicians	Physician/ population ratio	Number of physicians	Physician/ population ratio	Number of physicians	Physician/ population ratio	Number of physicians	Physician/ population ratio	Number of physicians	Physician/ population ratio	Number of physicians	Physician/ population ratio
Nfld.	154	1:2310	178	1:2130	199	1:2020	228	1:1850	241	1:1840	277	1:1682
P.E.I.	70*	1:1390	69	1:1460	83	1:1220	83	1:1190	81	1:1250	87	1:1207
N.S.	566*	1:1130	609	1:1080	642	1:1060	678	1:1030	712	1:1000	719	1:1013
N.B.	337	1:1530	353	1:1500	373	1:1460	378	1:1480	410	1:1420	445	1:1362
Quebec	4145	1: 970	4311	1: 980	4559	1: 980	4905	1: 960	5397	1: 920	5863	1: 883
Ontario	5523	1: 830	5822	1: 840	6400	1: 820	7064	1: 790	7409	1: 800	7908	1: 780
Manitoba	775	1:1000	799	1:1010	866	1: 960	912	1: 940	969	1: 910	1033	1: 879
Sask.	633	1:1310	713	1:1200	776	1:1130	835	1:1050	886	1:1010	895	1:1019
Alberta	780	1:1190	863	1:1150	963	1:1120	1041	1:1100	1141	1:1070	1280	1:1023
B.C.	1280*	1: 900	1418*	1: 870	1570	1: 840	1747	1: 830	1850	1: 840	2010	1: 810
Canada (excl. Yukon & N.W.T.)	14,263*	1: 975	15,135*	1: 968	16,431	1: 955	17,871	1: 928	19,096	1: 905	20,517	1: 879

*Estimated.

Sources: Physicians: C.M.A. Survey of Provincial Licensing Authorities.
Population (not shown): Estimated for December 31, from D.B.S. data.

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OBITUARIES

DR. MAURICE FOISY, 55, died at his residence in Montreal, Que., on September 24, 1961. He was educated at the Collège L'Assomption and the Collège Ste-Marie and graduated from the University of Montreal in 1935.

Dr. Foisy is survived by his widow.

DR. L. A. GIRARD, 90, died at Montreal on September 27, 1961. Dr. Girard was born in Dorion, Que. He took classical studies at Rigaud and studied medicine at the University of Montreal. Following his graduation, he practised medicine in Maine and Massachusetts and in 1921 returned to Montreal, Que.

He is survived by four sons and a daughter.

DR. J. R. GABY, 39, died on September 28, 1961, in Teston, Ont. He was educated at Upper Canada College and in 1945 graduated from the University of Toronto in medicine. He served with the Royal Canadian Medical Corps. Dr. Gaby specialized in ophthalmology and was a member of the Royal College of Physicians and Surgeons. He was an officer of the Academy of Medicine, and also served on the staff of the Hospital for Sick Children.

Dr. Gaby is survived by his widow and four daughters.

DR. CHARLES I. JUNKIN, 64, former chief anesthetist at the Hospital for Sick Children, died in the Toronto General Hospital on September 17, 1961.

Dr. Junkin was born in Fenelon Falls, Ont., and received his early education in Toronto. After serving four years in the Canadian Army during the First World War, he entered the medical school of the University of Toronto. He graduated in 1924 and practised as an anesthetist in North Toronto. In 1946 he served a term as chairman of the medical advisory board of the Hospital for Sick Children.

He is survived by his widow and four children.

DR. J. A. RANNIE, 87, died on October 14, 1961, at Norfolk General Hospital, Simcoe, Ont. A native of Chatham, Ont., he graduated from the University of Toronto in 1896. He practised in Florence, Ont., for several years before taking postgraduate studies in England and in Germany. Dr. Rannie practised in Chesley, Ont., until his retirement in 1940. He then moved to Port Rowan, Ont., where he served as a member of the local library board until 1959.

Dr. Rannie is survived by his widow and two sons.

DR. ENOCH LEE ROBERTS, 90, a native of Lynedoch, Ont., died in Toronto on September 22, 1961. He was gold medalist of the 1886 graduating class in medicine from the University of Toronto. Dr. Roberts pursued further studies at Johns Hopkins and specialized in eye, ear, nose and throat disease.

He practised first in Brantford, Ont., and then in Timmins, Ont. Besides his medical activities, he was a noted bridge player, and won a cup in a world bridge competition.

DR. LEOPOLD SAVAGE, general medical practitioner at St. Philomène and Montreal for more than 50 years, died at Montreal on September 24, 1961. He was born at Grande Rivière, Gaspé, Que., and graduated from Laval University in 1910. He practised medicine at St. Philomène de Chateauguay for 25 years, and was coroner for the Beauharnois district.

Dr. Savage is survived by one son, Dr. Léopold Savage, and one daughter.

DR. JOHN SHEAHAN, 90, died at the Hôtel-Dieu Hospital, St. Catharines, Ont., on September 27, 1961. Born in Norwich, Ont., he graduated from the University of Toronto School of Medicine in 1895. He practised in St. Catharines for 63 years. Dr. Sheahan was a pioneer in the treatment of tuberculosis, and was the first supervisor of the tuberculosis hospital in the Collier Homestead. Later he was president of the Board of Governors of this hospital, and the present Niagara District Sanatorium was built during his presidency. He was a past president of the Ontario College of Physicians and Surgeons, a life member of the Ontario Medical Association and chairman of the medical staff at Hôtel-Dieu Hospital. He served on the Senate of the University of Toronto and on the Separate School Board, and was a director of the Children's Aid Society. Dr. Sheahan was a past Grand Knight of the Knights of Columbus, and a Knight of St. Gregory.

He survived his wife and only daughter.

DR. GERALD A. SMITH, 46, died on September 12, 1961, in the Terra Nova area, Newfoundland, while on a hunting expedition. He was born at Twillingate, Nfld., did his pre-medical studies at Memorial University, and graduated from Dalhousie University in 1940. He interned at Saint John, N.B., and at Kentville, N.S. After this he practised medicine with his father, Dr. Cecil Smith, at Angle Brook, Nfld., and later joined his uncle, Dr. O. V. Smith, at Botwood, Nfld., carrying on the practice after the latter retired.

He is survived by his widow, a son and a daughter.

Le DR MARC TRUDEL, Président de la Commission du salaire minimum et Président du Collège des Médecins and Chirurgiens de la Province de Québec, est décédé le 10 septembre 1961, à l'âge de 65 ans à Shawinigan. Il obtint son degré en Médecine en 1922, de l'Université de Montréal. Il fut ministre d'Etat dans le cabinet Duplessis et député de St-Maurice à la Législature provinciale. Il fit ses débuts politiques en 1935. Il a exercé sa profession à Shawinigan durant 25 ans.

Le Dr Marc Trudel laisse dans le deuil neuf enfants.

DR. RALPH R. WITHROW, 71, died at Springhill, N.S., on September 25, 1961. Born in Upper Rawdon, Hants County, he attended school there, and later graduated from the Halifax Academy. In 1915 he graduated from Dalhousie University and went to Springhill, N.S., to practise surgery. Dr. Withrow was awarded a specialist's certificate in general surgery in 1946, and he was also a registered pharmacist in Springhill, N.S.

He is survived by his widow and two daughters.

BOOK REVIEWS

CANCER CHEMOTHERAPY. American Lecture Series. A Monograph in the Bannerstone Division of American Lectures in Living Chemistry. Edited by I. Newton Kugelmass. 253 pp. Illust. Charles C Thomas, Springfield, Ill., 1961. $10.50.

At a time when chemotherapy is in such vogue, it is fitting that a concise book on the chemotherapy of cancer should appear. This book stands apart as an authoritative, concise treatise on the subject and brings the field absolutely up-to-date from a practical point of view.

There are three excellent understandable chapters on basic considerations including historic features, the present status and the future; chemical background (complete with formulae) and modes of action including the vital problems of the effect of chemotherapeutic agents on the cellular metabolism and composition.

One chapter describes the workings of the cancer chemotherapy program and preclinical testing. Knowledge of this aspect of the problem is vital to an understanding of the approach to chemotherapy in the United States and to an insight into the methods of drug selection and evaluation. This scheme may serve as a model for co-operative studies involving many groups of workers striving toward the same goal with a reasonably charted course and a minimum of duplication in various centres.

Nine chapters deal with specific disease problems such as malignant lymphomas (in adults and in children), leukemias, multiple myeloma, solid tumours in children and in adults, mammary carcinoma and tumours of prostate, thyroid and adrenal. One chapter deals with local, systemic and regional chemotherapy as adjuvants to surgical treatment—a most topical subject.

The final chapter provides a service so vast that it virtually justifies the existence of the book (such final justification is not in the least necessary). This supplies selected references in clinical cancer chemotherapy—382 in all, some as recent as January 1960. These references in turn are indexed.

This is a book which fills admirably the need for an up-to-date evaluation of the effectiveness of a series of drugs in a field where evaluation of real worth is so notoriously difficult.

Limitations of drugs are stressed; dosage regimens are given. Bibliographies at the ends of chapters are excellent. To some this book may well be a standard day-to-day handbook; to others it will be an important and vital reference work.

EVALUATION OF THE CARCINOGENIC HAZARDS OF FOOD ADDITIVES. Fifth Report of the Joint FAO/WHO Expert Committee on Food Additives. Technical Report Series No. 220. 33 pp. World Health Organization, Geneva, Switzerland, 1961. $0.60.

This is an extremely important report, especially as the addition of various chemicals to foodstuffs is increasing at a rapid rate. At a conservative estimate about 1000 different substances have at the present time been, or are being, added to foods.

In many instances we simply do not know whether food additives are carcinogenic or not. Many experiments which have been done in the past have been inadequately designed and planned. But the most glaring defect is that governmental bodies are not spending enough money on evaluation of these substances. This is not the fault of the agencies concerned but of the legislators in many countries.

The difficulty of extrapolating the results of animal experiments to man are well known, especially in this exacting field of possible carcinogenesis.

Present needs include epidemiological studies on spontaneous tumour formation in animal colonies, appropriate biometric design of experiments, time and dosage levels for testing, and particularly the development of short-term biological tests for carcinogens. In Appendix 1 of the report a valuable list is given of a number of food additives and food contaminants considered by the Committee.

THE PHYSICS OF RADIOLOGY. American Lecture Series. 2nd ed. Harold Elford Johns. 767 pp. Illust. Charles C Thomas, Springfield, Ill., 1961. $23.00.

In the eight years since the publication of this text so many advances in knowledge have occurred in medical radiation physics that the second edition, now appearing, is in reality a new book. In fact, the original title "The Physics of Radiation Therapy" has been changed to "The Physics of Radiology".

The traditional topics of radiation physics are enlarged and expanded upon. Certain subjects not previously discussed have made their debut. Isotopes, rotational therapy, protection and radiobiology are now included, but as latecomers they are discussed somewhat more briefly than one might wish. This is particularly evident in the coverage of physical principles of diagnostic radiology. For example, only three pages are devoted to image amplifiers. Though brief, such diagnostic items as film characteristics, density, contrast and latitude are described. Screens and grids are discussed. Retinal physiology is described relative to fluoroscopy and image amplification, and useful material on patient dosage in diagnostic radiology is presented.

The emphasis throughout the book on photon energy and energy absorption reflects the most important change in approach that has come into this subject in recent years. The material is presented in a very clear style, and as various points are made, they are supported by specific examples, as well as by very liberal use of graphs, charts and line drawings.

At the end of each chapter, in addition to an authoritative bibliography, problems are set out, with answers provided at the end of the book. Over forty tables dealing with absorption coefficients, depth dose, roentgen to rad conversion, etc., are gathered together at the conclusion of the text.

In the preparation of any text there is an inherent difficulty in striking a happy medium to serve the different interests of practising radiologist and research radiation physicist. This has been accomplished and the text is recommended as essential for anyone dealing with medical radiology.

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CLINICAL AUDIOMETRY. English ed. Michel Portmann and Claudine Portmann. Translated by Bruce Proctor and Sheila Wevers. 349 pp. Illust. Charles C Thomas, Springfield, Ill.; The Ryerson Press, Toronto, 1961. $13.25.

This is an excellent book on the technical assessment of hearing by clinical audiometry which, until this present edition, has been available only in the French language. The Portmann Clinic, in Bordeaux, has long been considered one of the best centres for oto-laryngology in Europe, and the text represents the thoroughness with which the examinations are done in that it is almost entirely confined to those entering the division of otology as a specialty. It is not too long to serve as a reference book for undergraduate students in general, but would be of no particular value to the ordinary practitioner of medicine. There is very little within the text of this book on the important subject of auditory training, and one would think that this might have added to its usefulness.

CEREBRAL INFARCTION: THE ROLE OF STENOSIS OF THE EXTRACRANIAL CEREBRAL ARTERIES. Privy Council—Medical Research Council Special Report Series No. 300. 95 pp. Illust. Her Majesty's Stationery Office, London, 1961. 14s 0d. net.

This small monograph provides detailed anatomical evidence relating atherosclerosis, thrombosis and other obstructing lesions of the carotid, vertebral and cerebral arteries to cerebral infarction. Based on careful observation and records of a region that is usually not examined adequately at autopsy, this study of 100 cases documents these common lesions in a comprehensive manner. Individual anatomical diagrams and clinical summaries are given.

The authors discuss the relation of such stenotic lesions to cerebral infarction and comment on their pathogenetic role in synergism with hypotensive and hypoxic states leading to cerebral infarction. While the reviewer takes exception to some of the uncritical generalizations that are made and while it may be regretted that an appropriate control series was not also presented, the authors' treatment of the subject is sound and stimulating. The frequent existence of stenotic lesions of the extracranial cerebral arteries in patients with cerebral infarction deserves wide appreciation.

The monograph is recommended to all who want to understand the pathogenesis of cerebral infarction.

THE ROLE OF IMMUNIZATION IN COMMUNICABLE DISEASE CONTROL. World Health Organization Public Health Papers No. 8. V. M. Zhdaniv, R. Cruickshank, E. Edsall and J. de Moerloose. 118 pp. World Health Organization, Geneva; Columbia University Press, New York, 1961. $1.25. Also published in French.

Experience has shown that the only effective means of controlling and eradicating the communicable diseases is by active immunization. The history of diphtheria is an excellent illustration of this point. This publication brings together the latest information on the numerous toxoids and vaccines now available for active immunization. It is an excellent reference on the subject. There is a reference to quadruple vaccine (D.P.T. and Polio) that it is not recommended at present. This mixture has been used with excellent results in Canada, and is recommended for use by the provincial departments of health.

CARTER'S PRINCIPLES OF MICROBIOLOGY. 4th ed. Alice Lorraine Smith. 603 pp. Illust. The C. V. Mosby Company, St. Louis, Mo., 1961. $6.00.

This text represents a useful addition to the group of books suitable for undergraduates studying introductory medical microbiology. The principal features of all of the pathogenic micro-organisms have been well presented, together with a good general survey of the principles of epidemiology and infection control.

Although the author indicates in the preface that revision of the text required consideration being given to the remarkable advances in virology in recent years, only a very limited amount of basic information about the viruses is presented, and a very cursory description of tissue culture and the laboratory diagnosis of virus infections is included.

Nonetheless, the physician will find in this book a clear presentation of the fundamental features of medical microbiology, and it is certainly a text to be seriously considered for science undergraduates.

DERMATOLOGY FOR STUDENTS. Edited by Ray O. Noojin. 301 pp. Illust. Charles C Thomas, Springfield, Ill., 1961. $9.50.

This book deals predominantly with the common dermatoses seen daily by the dermatologist, and the ones most familiar to the general practitioner. These can also become readily recognized by the undergraduate medical student during his clinical instructions in the outpatient department. Each chapter covering a certain condition or a related group is the contribution of a well-known authority and the composition is clear, concise, and very readable. A chapter on syphilis is included and an excellent short introductory chapter on some of the basic sciences pertaining to the skin. The approach to each topic is direct and simple, covering morphological description, etiology and diagnosis. Therapy is kept to a minimum and is usually presented simply.

The publication also contains a very good colour atlas. It is certainly not a reference text-book. It is the type of text that the medical student will enjoy reading during his exposure to dermatology.

BASIC NEUROANATOMY. Carlton George Smith. 257 pp. Illust. University of Toronto Press, Toronto, 1961. $9.00.

There is a simplicity and beauty of form in this book which is attractive to the reviewer. The facts of relations of the neurons and nerve pathways are briefly stated. Function is discussed more than might be expected in such a small book. The drawings are excellent and give a good impression of relations in three dimensions. These are simple and accurate, and are not overloaded with data.

This is a book which is suitable for medical students and students in paramedical specialties who are studying neuroanatomy. The graduate student in the clinical neurological disciplines will find it helpful, even though he will need to read more widely. Graduate students in psychiatry and psychology should find it helpful in their work and in preparation for examinations. Teachers of neurology and neuroanatomy should find this book valuable, and the reviewer would recommend it to students.

(Continued on page 1174)

local analgesic action

strong broncho-dilator action

depressant action on cough mechanism

the right combination
to relieve a cough

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(Continued from page 1172)

MIDWIFERY. 10th ed. Edited by Frederick W. Roques, John Beattie and Joseph Wrigley. 739 pp. Illust. Edward Arnold (Publishers) Ltd., London; The Macmillan Company of Canada Limited, Toronto, 1961. $7.65.

This is the tenth edition of this well-known textbook of obstetrics. As mentioned in the preface, there has been much revision of the subject matter, particularly as regards abnormalities in presentation and medical diseases complicating pregnancy. Also, three new chapters have been added, one introductory chapter, one on blood transfusion in pregnancy, and one dealing with vital statistics.

As before, it is an exceedingly well-written book and easy to read. The subject of each chapter is well organized and, where applicable, a good classification is presented first and the subject then treated according to the classification. All facets of obstetrics are covered, some more thoroughly than others.

What makes the book easy to read is the clear, concise way things are said. This, and the introductory chapter, make it obvious that the book is directed at the medical student. Thus, ambiguity is avoided throughout. However, in order to do this, very little discussion is offered, even when controversial subjects are being dealt with. Also, the classification and management of difficult problems such as diabetes in pregnancy, accidental and inevitable hemorrhage, and many others, are too clear-cut. Owing to this oversimplification, the student will be left with the impression that every case falls accurately into one class and that each class has one type of treatment. As a result of this, throughout practically the whole book there is a dogmatic tone which may become irritating to some readers.

The only objection the reviewer has as regards the organization of the book concerns pelvimetry. The description of the pelvis and external pelvimetry are dealt with in Chapter 8, without measurements being given. However, classification of pelves and internal pelvimetry are dealt with in Chapter 32, after malpositions and malpresentations have been presented.

Despite this, the student who can afford a second textbook of obstetrics will find this one useful for review and quick reference. The postgraduate student will find it inadequate.

CHILD DEVELOPMENT AND CHILD PSYCHIATRY. Edited by Charles Shagass and Benjamin Pasamanick. 225 pp. Illust. The American Psychiatric Association, Washington, D.C., 1960. $2.00.

This is a collection of scientific papers and discussions of a Regional Research Conference held March 18-19, 1960, in Iowa City, under the joint auspices of the State University of Iowa College of Medicine, Department of Psychiatry and Psychopathic Hospital, and the American Psychiatric Association. The report is edited by a previous member of the McGill University staff, Charles Shagass, M.D., and also by Benjamin Pasamanick, M.D.

The conference was in tribute to Dr. Arnold Gesell in his eightieth year.

The text is made up of nine papers, all of a high standard, and some of crucial importance to the field of child development and child psychiatry. The tribute of Dr. Leo Kanner to Dr. Gesell is not only a historical background of great interest but a masterful and exciting work of English prose. Careful research of Knoblock and Pasamanick around the norms of the 40-week Gesell schedule will give reassurance to adopting agencies.

The current trend in child psychiatry to evaluate in a more detailed way the effects of the individual differences in personality development is covered by McCandless in an article entitled "Rate of Development, Body Build and Personality". The effects of early or slow sexual maturity are discussed and a good review of the literature is made available in the references.

Dr. E. J. Anthony, well known in British circles, now the Ittelson Professor of Child Psychiatry in Washington University School of Medicine at St. Louis, Missouri, once more presents an article on "Childhood Micropsia" and integrates the theories of perception of Piaget and Werner with those of Schilder and the psychoanalysts. This is an extremely skilfully prepared presentation. Other important papers are "Capacity of the Human Newborn for Mother-Infant Interaction" and "The Temporal Dimensions of a Neonate Response" by Helen Blauvelt and Joseph McKenna. This important work has come out of the Department of Pediatrics in Syracuse, New York. It is too bad that the paper cannot show the films which accompanied the presentation, as they are very convincing, showing micro-responses of behaviour in the mother-child relationship.

Other papers cover maternal behaviour and personality development; two approaches to the study of maternal attitudes; and conforming and deviating behaviour in the problem of guilt.

This is an interesting group of papers for all professional persons interested in child and family life.

PHYSIOLOGICAL RESPONSES TO ENVIRONMENTS. Special Report Series No. 298. Compiled by R. K. Macpherson. Her Majesty's Stationery Office, London, 1960. $6.53.

Following the fall of Singapore in the early part of the War, a study of the reports written by the Commanding Officers of H.M. ships revealed that during action in the tropics the temperature in many of the working spaces exceeded the range in which man can function. At the request of the Board of Admiralty, the Medical Research Council undertook a long-term study to determine the environmental temperatures and humidities which will limit physical activity in the tropics. This work was done in part at the Psychological Laboratory in Cambridge and at the National Hospital, Queen's Square, London, England. These findings were confirmed and extended later by tests at the Tropical Research Laboratory in Singapore.

The present volume is a compilation and assessment of this seven-year research program. It is a well-written analysis and discussion of a confusing mass of data. From this material the questions asked by the Board of Admiralty can be answered, but the answers are not simple, for there are many variables, each of which must be considered.

This volume will be of interest to a limited number of medical men, since it deals with problems of ventilation and environment and acclimatization under tropical conditions. However, it will become a standard reference work on this subject.

MEDICAL NEWS *in Brief*

(Continued from page 1161)

NEW FELLOWS OF THE AMERICAN COLLEGE OF SURGEONS

Approximately 1103 surgeons were inducted on October 5 as new Fellows of the American College of Surgeons in special ceremonies during the annual five-day Clinical Congress of the world's largest organization of surgeons. The American College of Surgeons, founded in 1913 to establish standards of competency and character for specialists in surgery, has grown in 48 years' time from a founding group of 450 to a total membership of approximately 24,500 in 71 countries.

Fellowship, entitling the recipient to the designation "F.A.C.S." following his name, is awarded to doctors who fulfil comprehensive requirements for acceptable medical education and advanced training as specialists in one or another of the branches of surgery, and who give evidence of good moral character and ethical practice.

Canadian recipients of Fellowships at the 1961 Convocation were:

Alberta: Kenneth G. Calvert, Calgary; Kenneth Baker, Ray G. Davis and William A. Maclean, Edmonton; Ernest D. MacCharles, Vernon W. Sobey and Jacobus A. van Belkum, Medicine Hat; George R. Burland, Olds.

British Columbia: Gerald Coursley, New Westminster; Allin H. Moore, Vancouver.

Manitoba: Werner P. Hirsch, Brandon; Morris H. Broder, James S. McGoey, Martin L. Robinson and Walter Zings, Winnipeg.

Nova Scotia: M. Thomas Casey and Douglas H. MacKenzie, Halifax.

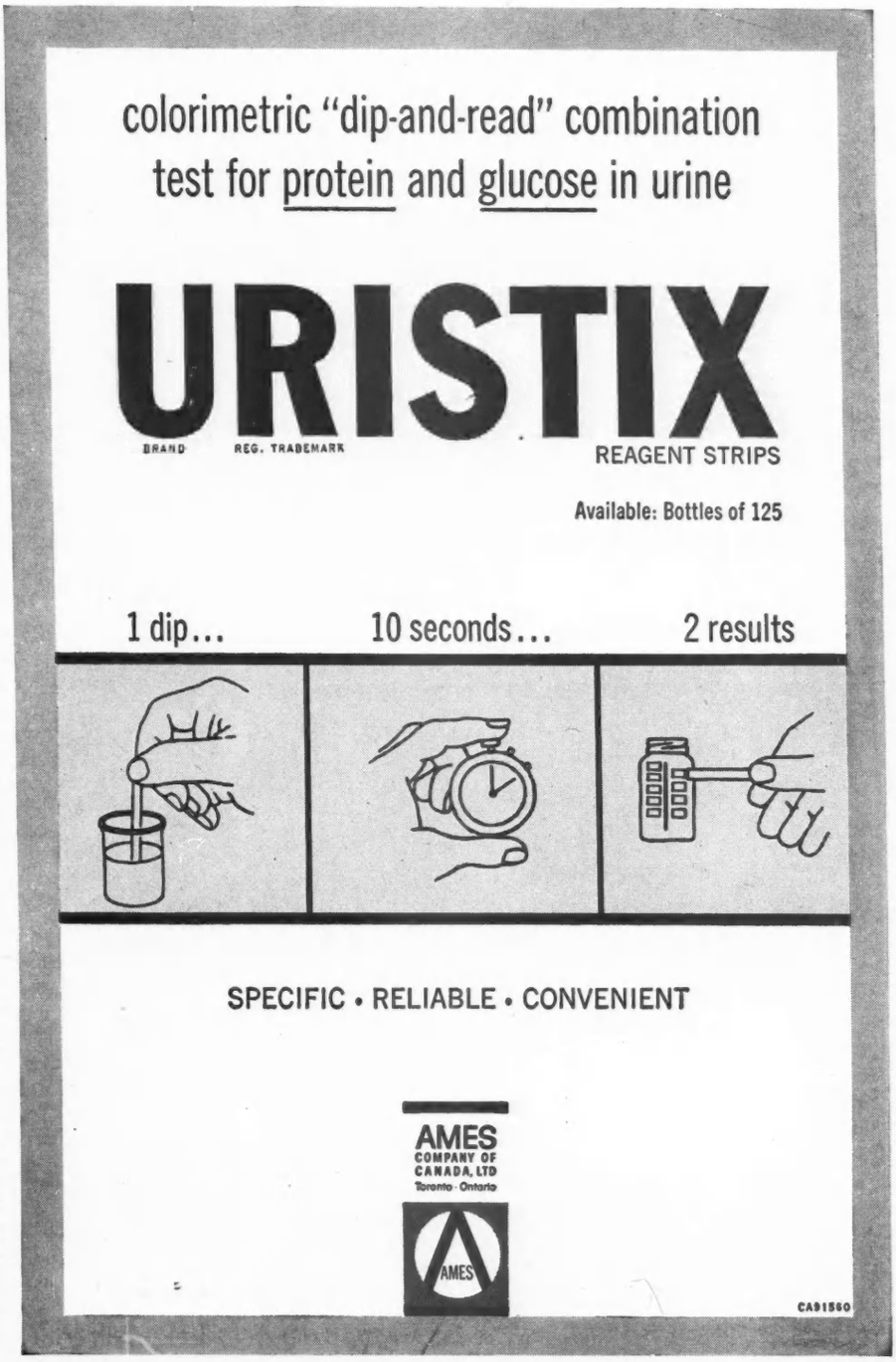
Ontario: James R. Digby, Brantford; David A. Rosen, Kingston; Gerard G. Lippert, Kitchener; C. William M. Service, Lindsay; William L. Tew and John A. McCredie, London; W. Gordon Beattie and J. Victor Berry, Ottawa; John T. R. Stewart, Peterborough; Philip B. McGarrity, Sarnia; William J. Kelly, Sault Ste. Marie; William J. Horsey, N. Tait McPhedran, John A. Palmer and Robert B. Salter, Toronto; Robert A. Haliburton, Gordon L. Henderson, Charles A. Laing, Norman L. Marshall and Joseph M. Schulde, Windsor.

Québec: Georges A. Daigle, Lévis; François Archambault, Albert A. Butler, Sacha I. Dimintrov, David Elkin, William H. Feindel, John W. Gerrie, Lawrence G. Hampson, Léon Heller, Luc Lafortune, Louis LaPorte, Darrell D. Munro et Edward G. O'Brien, Montréal; André B. Marquis, Roland Scherrer et Ian C. Wilson, Québec; Léon Demers, Sherbrooke; Maurice Duhaime et André Martel, Trois-Rivières.

AMERICAN SOCIETY OF MAXILLOFACIAL SURGEONS

The Annual Meeting of the American Society of Maxillofacial Surgeons will be held in Montreal, Que., on May 27 to 30, 1962, at the Queen Elizabeth Hotel. Further information from: Edward C. Hinds, D.D.S., M.D., Secretary-Treasurer, P.O. Box 2006B, Houston 25, Texas.

(Continued on page 36)



MEDICAL NEWS *in brief*

(Continued from page 35)

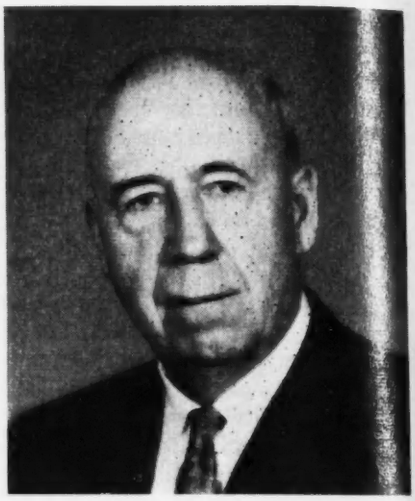
SECOND CANADIAN MENTAL HEALTH SERVICES INSTITUTE

The Second Canadian Mental Health Services Institute, sponsored by the Canadian Psychiatric Association, will be held at the Château Laurier, Ottawa, from January 15 to 18, 1962. The theme of the Institute will be "Mental Health Services for Canada—Examination of the 1961 C.M.H.A. Report". Further information is available from: Dr. V. E. Chase, Chairman, Planning Committee, c/o Canadian Psychiatric Association, Suite 103, 225 Lisgar Street, Ottawa, Ont.

—

DR. M. R. MacCHARLES ELECTED CHAIRMAN OF T.C.M.P.

Dr. M. R. MacCharles of Winnipeg, former Vice-Chairman and a member of the Commission for five years, was elected chairman of Trans Canada Medical Plans at the annual meeting in June. Dr. MacCharles has headed a number of committees of T.C.M.P. and is well qualified to take over his new responsibility.



Dr. M. R. MacCharles

Other officers elected at the annual meeting were: Dr. J. A. MacDougall, Saint John, Vice-Chairman; Dr. J. O. Lockhart, Hamilton, Honorary Secretary; Mr. A. L. McLellan, Vancouver, Honorary Treasurer; and Mr. C. Howard Shillington, Toronto, Executive Director.

—

UNPREDICTABILITY OF POLIOMYELITIS ANTIBODY RESPONSE OF INFANTS

The response of infants to antigenic stimulation is variable. In part, this is due to the inability of the small infant to respond immunologically as do the older child and adult. The extent to which passively transferred antibodies interfere with active immunization with living or dead poliovirus vaccines is not clear.

A study by Cramblett and Fomon (*J. Pediat.*, 58: 779, 1961) was undertaken to obtain more information about the response of infants to antigenic stimulation with poliomyelitis vaccine and the influence of passively transferred antibodies. Serial determinations of antibody titres against the three types of poliovirus have been performed before, during and after the course of inoculation of 45 normal, full-term infants with Salk vaccine.

Salk poliomyelitis vaccine was administered according to two

(Continued on page 38)

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581

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1. Meyer, O. O.: Postgrad. Med. 24:110, Aug., 1958. 2. Baer, S., et al.: J.A.M.A. 167:704, June 7, 1958. 3. Moser, K. M.: Disease-a-Month, Chicago, Yr. Bk. Pub., Mar., 1960, p. 13.

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COUMADIN* (warfarin sodium) is available as: Scored tablets—2 mg., lavender; 2½ mg., orange; 5 mg., peach; 7½ mg., yellow; 10 mg., white; 25 mg., red. Single Injection Units—one vial, 50 mg., and one 2 cc. ampul Water for Injection; one vial, 75 mg., and one 3 cc. ampul Water for Injection.

Average Dose: Initial, 40-60 mg. For elderly and/or debilitated patients, 20-30 mg. Maintenance, 5-10 mg. daily, or as indicated by prothrombin time determinations.

*Manufactured under license from the Wisconsin Alumni Research Foundation.

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MEDICAL NEWS *in brief*

(Continued from page 36)

regimens. The infants in Group A were given the first injection at the age of 10 weeks (median), the second at 14 weeks, the third at 40 weeks, and the fourth at 60 weeks. Infants in Group B received their first injection at 6 weeks (median), the second at 10 weeks, the third at 14 weeks, and the fourth at 40 weeks of age.

All infants of Group A had serum titres of neutralizing antibodies of 1:4 or greater one month after the fourth injection which was given at 57 to 64 weeks of age.

Three of 13 infants of Group B had titres of neutralizing antibodies of less than 1:4 against one or more of the three types of poliovirus one month after the fourth inoculation given between 36 and 45 weeks of age.

A titre of passively transferred neutralizing antibodies of 1:6 or greater at the time the first inoculation was given seemed to interfere with response to active immunization.

—

NICOLO CASTELLINO FOUNDATION III INTERNATIONAL PRIZE

The Nicolo Castellino Foundation is offering a prize, open to competition, for an original, unpublished work on occupational medicine, the subject to be freely selected by the author and the presentation to be of strictly scientific character. Persons engaged in occupational medicine, whether Italian or foreign, may compete provided they are not university professors teaching occupational medicine and are not over 40 years of age on December 31, 1962. Persons working in collaboration with others may compete. The prize is one million Italian lire (approximately $1670) and may not be divided.

The Foundation reserves the right not to award the prize if the submissions, in the opinion of the jury, do not attain proper standards.

The paper must be written in one of the following languages: Italian, French, German, English, Spanish or Portuguese, and must be submitted in seven typed copies before December 31, 1962, to the Secretary of the Foundation. The paper must not be signed by the author but must bear a pseudonym. A sealed envelope must accompany the submission containing the following information: the name and address of the author, documentary evidence of the author's age; a statement by the author to the effect that the work reported is original, unpublished and has not been submitted in any other competition. If a submission does not meet these conditions it will not be allowed in the competition.

The jury will reach its final decision about April 1963. The announcement of the winner's name will be made at the time of the XIV International Congress on Labour Medicine to be held in Madrid in the second half of 1963. The prize will be paid to the author one month after the Congress closes.

Further details may be obtained by writing the Secretary, Nicolo Castellino Foundation, via IV Novembre 144, Rome, Italy.

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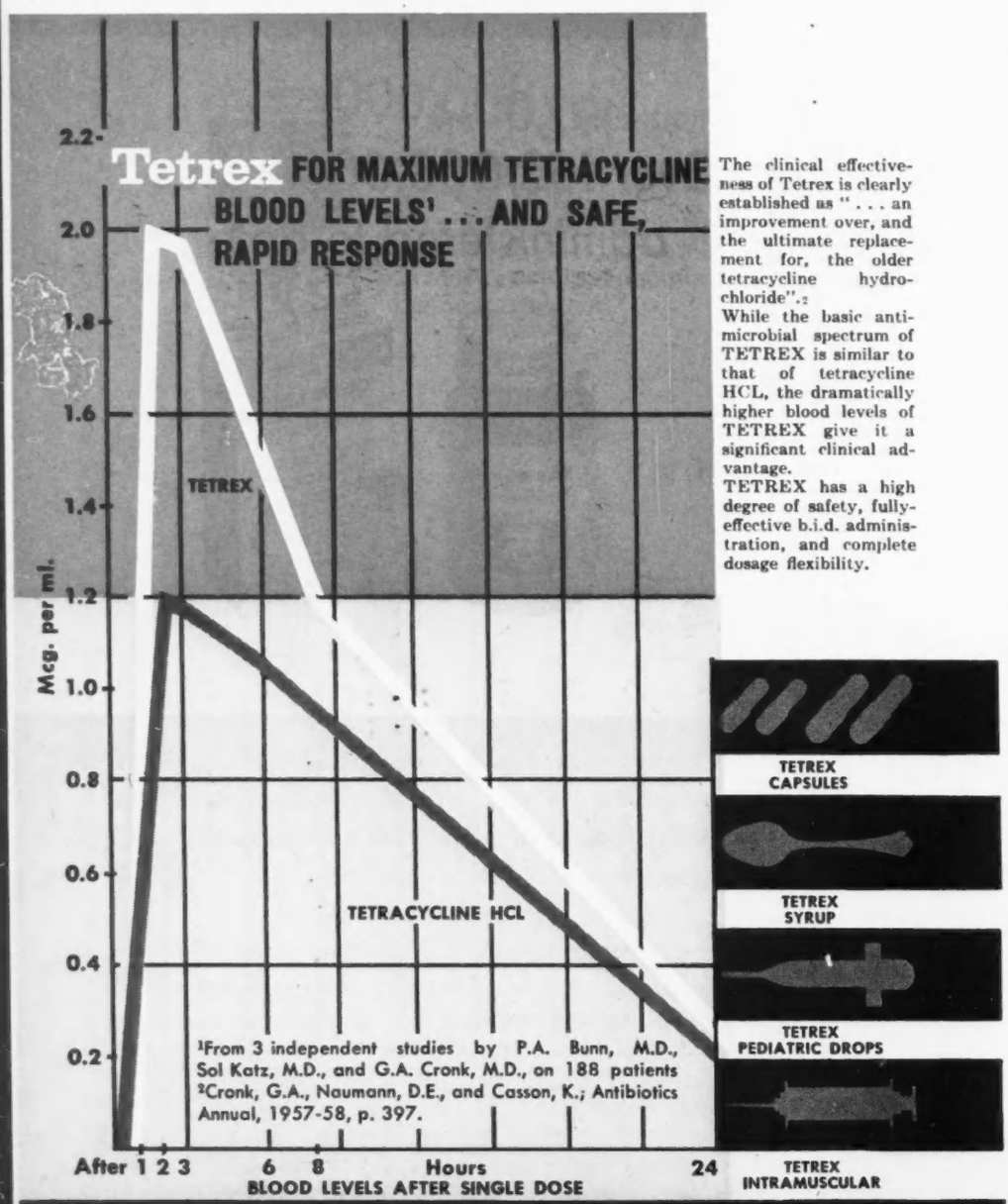
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MEDICAL NEWS *in brief*
(Continued from page 38)

MORE ON TRAFFIC SAFETY

Some of the current research to improve traffic safety that is being carried out at the Road Research Laboratory of the British Department of Scientific and Industrial Research is of interest to physicians and others concerned with the rising toll of traffic injuries and fatalities. The following abstract (*Nature*, 191: 644, 1961) does not deal with the studies being done on materials and methods of highway construction but describes some advances in automobile design.

"The greater resistance to skidding, and the shorter braking distances, that can be achieved with tyres having tread rubber with a high hysteresis loss was demonstrated by two identical cars. [Tires with a high hysteresis loss can grip the surface of the road more efficiently. The exact definition of this in physical terms was beyond us.—Editor]. The cars were driven one following the other and about 30 ft. apart, at a speed of about 40 miles per hour on a wet, slippery section of the track. At a given signal, each driver applied his brakes as in an emergency stop; the car equipped with conventional tyres travelled farther in coming to rest than the one fitted with tyres with tread rubber with a high hysteresis loss. Experiments have shown that by this means braking distance can be reduced by about 14 per cent.

"Another series of demonstrations showed the advantages of fitting devices which prevent wheels from locking when brakes are applied. A car was driven at 45 miles per hour on a wet surface, and the driver applied his brakes as hard as possible to lock the wheels. When using Maxaret units to prevent wheel locking, the driver did not lose directional stability and was able to retain steering control and bring the car to a stop in a much shorter distance.

"To help analyse the cause of accidents the laboratory is using a camera suspended on a 40-ft. collapsible pole which protrudes from the roof of a van. The camera photographs, from above, the exact position of vehicles that have been involved in an accident. By this means it is hoped to obtain information on deficiencies in vehicle design and road layout.

"The laboratory has been cooperating with the glass industry in attempts to improve vision through toughened glass windscreens when they shatter. By reducing the fragmentation of the glass to between five and ten particles per inch in the part of the windscreen immediately in front of the driver he is given reasonable vision when the glass is shattered. The effectiveness of the new glass was demonstrated by driving a car with a shattered windscreen and maneuvering it around obstacles at about 20 miles per hour.

"The problem of getting information across to road users in the most efficient way was shown by a demonstration in the central area. Signs were mounted on a car which was driven towards the spectators, who were then invited to record by pressing push-buttons when they could read the signs; the distances at which they could do this were clearly indicated. Signs with different types of lettering were used."

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